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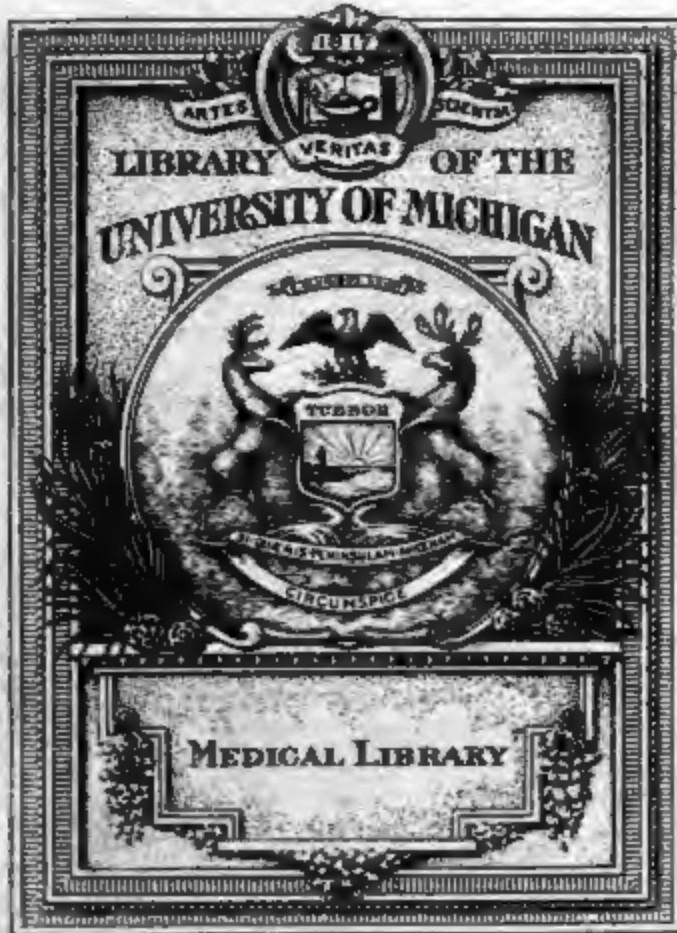
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VACCINATION AND ITS RELATION TO ANIMAL EXPERIMENTATION

JAY FRANK SCHAMBERG, M.D.
PHILADELPHIA

DEFENSE OF RESEARCH PAMPHLET I

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"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

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VACCINATION AND ITS RELATION TO ANIMAL EXPERIMENTATION

JAY FRANK SCHAMBERG, M.D.

PHILADELPHIA

[EDITORIAL NOTE—The choice of Dr. Schamberg to write this pamphlet is a most fitting one. Through his connection with the Municipal Hospital of Philadelphia he has had an unusually extensive experience with smallpox and has had the opportunity of observing vaccinated and unvaccinated persons after they have been exposed to this disease. He is the author of works on skin diseases and of many articles on the subject in medical periodicals. He is Chairman of the Vaccination Committee of the Pennsylvania State Medical Society, holds professorial positions in several medical schools, and is recognized as one of the most earnest students of vaccination in this country.]

VACCINATION

Thomas Jefferson, writing in 1806 to Edward Jenner, the discoverer of vaccination, said: "Future nations will know by history only that the loathsome smallpox has existed and by you has been extirpated." The prediction of this sagacious statesman would ere this have been fulfilled if vaccination and revaccination had been universally practiced. Despite one hundred years of incontrovertible testimony of the efficacy of adequate vaccination as a safeguard against smallpox, and despite an almost complete unanimity of opinion among scientific medical men of the century, there still remain some laymen and a few physicians who dissent from the generally accepted view.

In writing, therefore, on the increase of our knowledge of vaccination and smallpox in its relation to animal experimentation and research, it will be desirable to preface the same by a discussion of the efficacy of vaccination as a prophylactic measure against smallpox.

In order to appreciate the importance of Jenner's discovery of vaccination, it is necessary to comprehend how extensive and fatal was smallpox in the prevaccination period.

The date of the origin of smallpox, as is true with many of the pestilential diseases, is involved in some obscurity. While there are references in literature to diseases suggestively corresponding to smallpox dating back many centuries, we have no trustworthy record of the extent of its prevalence before the fifteenth century. The probabilities are that it made its first appearance in the Orient and was thence introduced into Western Europe. Epidemics of this disease became progressively more common during the seventeenth century and reached their maximum of frequency and extent in the eighteenth century. For official data concerning the disease in the seventeenth and eighteenth centuries we are largely indebted to the London "Bills of Mortality," which gave a weekly account of burials and christenings, and from 1629 to 1845 the specific causes of death, including smallpox.

It has been estimated that the population of London in 1685 was 530,000; in 1750 it was approximately 653,900; in 1801 it was determined by census to be 746,233.

The mortality from smallpox in London for an average of ten years, from 1681 to 1690, was over 3 per thousand of population (3,000 per 1,000,000); in the seventeenth and eighteenth centuries it frequently rose to 4.5 or more per thousand.

In the 54 years from 1647 to 1700, there was an average mortality from smallpox in London of 1,079 per year. The average yearly deaths by smallpox in the eighteenth century were 1,958. As it has been computed that about one in five died, it would appear that there were on an average over 5,000 cases of smallpox annually in the English capital in the seventeenth century, and almost 10,000 cases a year in the eighteenth century.

As will be readily comprehended, smallpox was a great scourge before the days of vaccination; but a small percentage of people escaped its ravages. It is asserted by contemporaneous writers that in the eighteenth century. At the end of certain epidemics, as many as 80 to 90 per cent. of the population represented survivors from attacks of smallpox.

Indeed, smallpox was as prevalent in the eighteenth century as measles is at the present time. Haygarth gives an account of an epidemic of smallpox in Chester, England, in 1744, at which time, out of a population of

14,713, 1,202 persons took the disease and 202 died. At the termination of the epidemic there were but 1,060 persons, or 7 per cent. of the population who had never had smallpox.

In 1722 smallpox devastated the small English town of Ware, whose population numbered 2,515 souls; of this number, there were only 914 persons susceptible to smallpox, inasmuch as 1,601 had already passed through an attack of the disease. During the epidemic referred to, 612 persons were attacked, leaving but 302 individuals in the entire town who had never had smallpox. Eighty-five per cent. of the population, therefore, were smallpox survivors.

With these official figures in mind, we may be better able to appreciate the general estimate of the extent of smallpox given by writers of the day. In 1802 Admiral Berkeley, in a speech before the House of Commons, said:

It is proved that in this United Kingdom alone 45,000 persons die annually of the smallpox; but throughout the world what is it? Not a second is struck by the hand of Time but a victim is sacrificed upon the altar of that most horrible of all disorders, the smallpox.

King Frederick William III, of Prussia, in a dispatch, dated Oct. 31, 1803, stated that 40,000 people succumbed annually to smallpox in his kingdom.

The French physician, De la Condamine,¹ stated that "every tenth death was due to smallpox, and that one-fourth of mankind was either killed by it or crippled or disfigured for life."

Juncker, professor of medicine in Halle in 1796-98, gathered statistics² indicating that 65,220 persons died of smallpox in the German-speaking countries in 1796.

Sarcone³ estimated the number of persons in Italy who suffered from smallpox as nine-tenths of the population. He states that in Rome in 1754 smallpox destroyed more than 6,000 lives.

Smallpox was introduced into the western hemisphere by the Spaniards about fifteen years after the discovery of America; in Mexico within a short period 3,500,000 persons are said to have died of the disease.⁴

1. De la Condamine: *Mémoire sur l'inoculation de la petite vérole*, 1754.

2. Kübler: *Geschichte der Pocken und der Impfung*, 1901, p. 99.

3. Sarcone: *Childpox*, etc., translated from the Italian into German by Lentini, Goettingen, 1782.

4. Chapman: *Eruptive Fevers*, etc., 1844. quoting Robertson's *History of the Discovery of America*.

It is alleged that in Mexico smallpox has exterminated whole tribes of Indians, sparing no one to tell the story of the annihilation.

Robertson refers to smallpox among the South American Indians as follows:⁵

In consequence of this [various calamities], together with the introduction of the smallpox, a malady unknown in America, and extremely fatal to the natives, the number of the people both in New Spain and Peru was so much reduced that in a few years the accounts of their ancient population appeared almost incredible.

Catlin⁶ states that, of 12,000,000 American Indians, 6,000,000 fell victims to smallpox.

Washington Irving's "Astoria" makes mention of terrible epidemics of smallpox among the Indians in which "almost entire tribes were destroyed."

Lloyd, who translated Prince Maximilian's "Travels in the Interior of North America," states in the preface, in reference to a smallpox epidemic among the Indians in 1837:

The Big-Bellied Indians and the Ricarees, lately amounting to 4,000 souls, were reduced to less than the half. The Assiniboins, 9,000 in number . . . are, in the literal sense of the expression, nearly exterminated.⁷

According to records published by the government of Denmark, a devastating epidemic of smallpox appeared in Iceland in 1707 which destroyed 18,000 out of the 50,000 inhabitants; 36 per cent. of the total population perished. It is stated on good authority that in the Danish colony of Greenland, in 1734, 6,000 to 7,000 persons perished from smallpox, representing nearly two-thirds of the population. The disease was introduced by a Danish ship.

The natives of New England likewise suffered great losses by smallpox. Robertson writes:

At the same time, about 1631, the smallpox, a distemper fatal to the people of the New World, swept such multitudes of the natives that some whole tribes disappeared.

In 1752 Boston had a severe epidemic of this dread disease. The population of Boston at that time was

5. Robertson, William: History of the Discovery and Settlement of America. 1829, p. 348.

6. Catlin: Letters and Notes on the Manners, Customs and Conditions of the North American Indians, London, 1841.

7. Extracts from a paper prepared by Sir. John Simon in 1857, and presented by him before the Royal Commission on Vaccination in 1889, Appendix No. 1, p. 63.

15,684; of this number, 5,998 had previously had smallpox. During the epidemic 5,545 persons contracted the disease in the usual manner, and 2,124 took it by inoculation. Eighteen hundred and forty-three people escaped from the town to avoid the danger of infection.⁸ There were, therefore, left in the city but 174 people who had never had smallpox. The population at the end of the epidemic practically consisted of persons who had survived an attack of this fear-inspiring malady.

CHANGE IN THE AGE INCIDENCE OF SMALLPOX

Smallpox was essentially a disease of children in former times; to such an extent was this true that the disease was called *Kindspocken* (childpox, or *Kindsblattern*). Owing to the pronounced contagiousness of the disease and the almost universal susceptibility to it, smallpox was largely contracted during child life, as measles is at the present time. But comparatively few adults contract measles at the present day because they are protected by a previous attack in infancy or childhood. The same conditions obtained with relation to smallpox in the days before vaccination. The adult population represented mostly the survivors from smallpox in childhood. It was estimated that only about 5 per cent. of persons were naturally insusceptible to the disease. Vaccination has totally changed the age period of smallpox. It is now excessively rare for a successfully vaccinated child under five years of age to die of the smallpox; it is even uncommon for a successfully vaccinated child under ten years of age to die of the disease, as was adequately proved in the testimony presented before the British Royal Commission on Vaccination.

The almost exclusive mortality of smallpox among infants and children in the days before vaccination is exemplified in the smallpox statistics of Kilmarnock from 1728 to 1764, a period of thirty-one years. During this time the total deaths were 3,860, and the deaths from smallpox 622. There were nine epidemics of smallpox recurring at intervals of about four years. Of the 622 smallpox deaths, 586 were in children under six years of age, 27 occurred in persons over the age of six, and the age of nine persons were not known.

In Chester, in the epidemic of 1774, all of the smallpox deaths, numbering 202, occurred in children under ten years of age and one-quarter of them under one year.

In Kilmarnock, of 622 deaths from smallpox between 1728 and 1763, only seven were of those above ten years.

In 1733 Warrington sustained an epidemic of smallpox which resulted in 211 deaths (population 8,000). In 1893 another epidemic occurred which resulted in 62 deaths (population 54,084, of whom 53,645 were vaccinated). The ages of the patients attacked are given in Table 1.

TABLE 1.—AGE OF SMALLPOX PATIENTS IN WARRINGTON,
1773 AND 1893

Age.	1773	Vaccinated.	Not Vaccinated.	* 1893
Under 1 year.....	49	0	8	
1 to 2 years.....	84	0	1	
2 to 3 years.....	33	0	0	
3 to 4 years.....	18	0	1	
4 to 5 years.....	15	0	1	
5 to 6 years.....	4	0	0	
6 to 7 years.....	2	0	0	
7 to 8 years.....	2	0	0	
8 to 9 years.....	4	1	1	
9 to 15 years.....	0	1	1	
15 to 20 years.....	0	1	2	
20 to 30 years.....	0	10	4	
30 to 60 years.....	0	24	5	
Over 60 years.....	0	1	0	
	<hr/> 211	<hr/> 38	<hr/> 24	

* Under 1 month.

In 1773 all of the deaths were under ten years and nine-tenths were under five years of age.

In 1893 among the vaccinated not a death occurred under eight years of age; indeed, not one vaccinated child under eight years of age contracted smallpox.

BLINDNESS AFTER SMALLPOX

People hold smallpox in great dread with good reason. Not only does this disease destroy life, disfigure and maim, but in the past it has been one of the most common causes of blindness. The early records of the London Asylum for the Indigent Blind showed that two-thirds of the inmates had lost their sight through smallpox.⁹

According to Sir William Aitkin, 90 per cent. of the cases of blindness encountered in the bazaars of India are due to smallpox.

Surgeon-General Pinkerton, in the service of the government of India, testified before the Royal Commission on Vaccination that blindness after smallpox was so common in India that a new word, "Kanu," was added to the Scindi language, the word meaning blindness in one eye.

Dr. Thomas W. Grimshaw, Registrar General for Ireland, testified before the commission that "the number of cases in which blindness is attributed to smallpox diminished from 725 in 1861 to 359 in 1881."

TABLE 2.—BLINDNESS FROM SMALLPOX IN IRELAND

Year.	—Blind in Ireland—		Total No. Deaths From Smallpox	Ratio to in Preceding 10 Years.	Cases in Which Blind- ness was ascribed to Smallpox.	Ratio to Total Number of the Blind.
	No.	Population.				
1851	7,587	1 in 864	38,275			
1861	6,879	1 in 843	12,727	725	1 in 9.5	
1871	6,347	1 in 852	2,852	526	1 in 12	
1881	6,111	1 in 847	7,550	359	1 in 17	

In the Municipal Hospital of Philadelphia during a period of over 35 years, but two smallpox patients have left the institution totally blind. Many patients with severe smallpox lose both of their eyes, but fortunately these patients usually succumb to the disease. The loss of one eye is, however, by no means rare. In the epidemic of 1901-1904 (which was not particularly severe), during which over 3,500 cases of smallpox were treated, 17 patients suffered the loss of an eye, despite most careful treatment; most of these patients were unvaccinated.

DECLINE OF SMALLPOX AFTER THE INTRODUCTION OF VACCINATION

In most of the countries of western Europe there was noted about the beginning of the nineteenth century a sudden and pronounced decrease in the morbidity and mortality of smallpox. Inasmuch as this was coincident with the diffusion of the practice of vaccination, there is strong reason to regard Jenner's epoch-making discovery as the causative influence. The careful records of smallpox mortality which were kept in various countries, particularly in Sweden and England, make it possible to prove by documentary evidence that a marvelous decrease in the deaths from smallpox occurred within a short period after the introduction of vaccination. In the twenty-eight years before vaccination in Sweden there died each year from smallpox out of each 1,000,000 of population 2,050 persons; during the forty years fol-

TABLE 3.—ANNUAL SMALLPOX DEATHS IN SWEDEN BEFORE
AND AFTER THE INTRODUCTION OF VACCINATION *

Before vaccination		1805	1,090
1749†	4,453	1806	1,482
1750	6,180	1807	2,129
1751	5,546	1808	1,814
1752	10,302	1809	2,404
1753	8,000	1810‡	824
1754	6,862	1811	689
1755	4,705	1812	404
1756	7,858	1813	547
1757	10,241	1814	308
1758	7,104	1815	472
1759	3,910	1816	690
1760	3,568			
1761	5,731			
1762	9,389			
1763	11,662			
1764	4,562	1817	242
1765	4,697	1818	305
1766	4,092	1819	161
1767	4,189	1820	143
1768	10,650	1821	37
1769	10,215			
1770	5,215			
1771	4,362			
1772	5,435			
1773	12,130	1822	11
1774	2,065	1823	39
1775	1,275	1824	618
1776	1,503	1825	1,243
1777	1,943	1826	625
1778	6,607	1827	600
1779	15,102	1828	257
1780	3,374	1829	53
1781	1,485	1830	104
1782	2,482	1831	612
1783	3,915	1832	622
1784	12,456	1833	1,145
1785	5,077	1834	1,049
1786	671	1835	445
1787	1,771	1836	138
1788	5,462	1837	361
1789	6,764	1838	1,805
1790	5,893	1839	1,934
1791	3,101	1840	650
1792	1,939	1841	237
1793	2,103	1842	58
1794	3,964	1843	9
1795	6,740	1844	6
1796	4,503	1845	6
1797	1,733	1846	2
1798	1,357	1847	13
1799	3,756	1848	71
1800	12,032	1849	341
1801	6,057	1850	1,376
		1851	2,488
Total (53 years) ..	125,130	1852	1,534
After Vaccination		1853	279
1802	1,533	1854	204
1803	1,464	1855	41
1804	1,460			

* The population in 1751 was 1,785,727; in 1855, it was 3,639,332.

† From 1749 to 1773 inclusive, deaths from measles are included.

‡ First successful vaccination in Stockholm.

TABLE 4.—POPULATION, TOTAL DEATHS, AND DEATHS BY SMALLPOX DURING SEVEN YEARS BEFORE THE GENERAL INTRODUCTION OF VACCINATION IN PRAGUE *

Year.	Population.	Deaths		Remarks.
		Total Number.	From Smallpox.	
1796	3,003,346	92,242	6,686	The proportion of the deaths generally to population.—1 :32.
1797	2,991,346	86,855	1,988	
1798	3,045,926	84,743	3,105	
1799	3,041,608	99,079	17,587	Deaths from smallpox to population.—1 :396 $\frac{2}{3}$.
1800	3,047,740	110,730	17,077	
1801	3,036,481	105,576	3,169	Deaths from smallpox to the total number of deaths.—1 :12 $\frac{1}{3}$.
1802	3,111,472	85,460	4,029	
Total...	21,278,055	664,685	53,641	
Average	3,039,722 1/7	94,955	7,663	

* Figures of the Medical Faculty of the University of Prague. Published in Papers on Vaccination issued by the London Board of Health, 1857.

TABLE 5.—POPULATION, TOTAL DEATHS, AND DEATHS BY SMALLPOX DURING TWENTY-FOUR YEARS SUBSEQUENT TO INTRODUCTION OF VACCINATION IN PRAGUE *

Year.	Population.	Deaths	
		Total No.	From Smallpox.
1832.....	3,888,828	139,061	807
1833.....	121,679	533
1834.....	3,945,875	122,171	285
1835.....	122,952	337
1836.....	124,015	291
1837.....	4,027,581	141,982	104
1838.....	108,419	62
1839.....	121,400	128
1840.....	4,145,715	118,471	699
1841.....	116,575	697
1842.....	124,019	339
1843.....	4,285,730	142,876	332
1844.....	113,184	150
1845.....	178,826	62
1846.....	4,480,661	132,379	59
1847.....	134,490	9
1848.....	141,409	115
1849.....	4,613,080	131,493	383
1850.....	176,211	478
1851.....	133,245	508
1852.....	134,921	343
1853.....	124,617	42
1854.....	4,593,770	124,746	68
1855.....	124,764	64
Total....	33,985,240	3,153,905	6,895
Average.	4,248,155	131,412 17/24	287 1/24

* The proportion of the total number of deaths to population. 1 :32 $\frac{1}{3}$. The deaths from smallpox to population, 1 :14,741 $\frac{1}{3}$. Deaths from smallpox to total number of deaths, 1 :457 $\frac{3}{4}$.

lowing vaccination, out of each 1,000,000 of population the smallpox deaths annually averaged 158.

During the seven years preceding the introduction of vaccination in Prague, smallpox caused one-twelfth of the total number of deaths; during the twenty years following the introduction of vaccination, smallpox caused but one four-hundred-and-fifty-seventh of the total number of deaths.

ARGUMENT OF OPPONENTS OF VACCINATION

The opponents of vaccination—and they have been with us since the days of Jenner—admit the decline in smallpox referred to, but deny that the decrease was the result of vaccination. They declare it was due rather to the discontinuance of inoculation. This argument was carefully considered by the British Royal Commission on Vaccination. There can be no question that smallpox prevailed to a greater extent during the eighteenth century than during any period of which we have records. We must, furthermore, admit that the practice of inoculation tended to diffuse the infection of smallpox, inasmuch as inoculated smallpox was contagious and could be contracted much in the same manner as natural smallpox. The effect of inoculation was really twofold in character: It tended, on the one hand, to lessen the number of deaths from smallpox by producing a mild form of the disease, accompanied by mortality varying between 0.3 per cent. and 2 per cent., and by conferring protection against the dangerous natural smallpox. On the other hand, it tended to perpetuate smallpox in the community by reason of the fact that the inoculated persons, often scarcely ill, disseminated the disease among others. The lessening of the death-rate by protection from natural smallpox, on the one hand, and the tendency to diffuse the disease, on the other hand, constitute two opposing influences which largely neutralize each other as far as the aggregate number of deaths from smallpox is concerned.

Unfortunately for the contention of the opponents of vaccination, the increase in the prevalence of and mortality from smallpox during the eighteenth century was not coincident in point of time with the introduction and extent of employment of inoculation.

Inoculation was introduced into England in 1721, but comparatively few persons were inoculated before 1725. As is admitted by the two dissenting members of

the Royal Commission on Vaccination, inoculation had no effect on the mortality from smallpox in the first quarter of the century (see page 354, Report of Dissentients, Sydenham Publication). Computation discloses the fact that from 1700 to 1725 the average yearly mortality from smallpox in London was 1,752. During the last quarter of the century, 1775 to 1800, when inoculation was much in vogue, the average yearly mortality was 1,817, an entirely insignificant increase. Indeed, relative to the population the smallpox deaths were actually less during the latter period.

It has been, furthermore, alleged by the opponents of vaccination that the decline in the prevalence of smallpox at or about the beginning of the nineteenth century was the result of improvement in sanitary conditions. It may be conceded that such improvements as better drainage and sewerage, freer ventilation, purer water-supply, lessened crowding in dwellings, and the like, would, by improving the average individual health, tend to lessen the fatality of all infectious diseases, not excluding smallpox. But such influences are totally inadequate to explain the striking and progressive decline in the prevalence of and mortality from smallpox that followed the introduction of vaccination.

If sanitary improvements were responsible for the lessened mortality from smallpox, why did they not similarly influence the mortality from measles, scarlet fever, and whooping-cough, which are favored by the same conditions that aid the dissemination of smallpox? Smallpox and measles resemble each other in the sense that the spread of both diseases is not dependent on any special sanitary defect. Unlike typhoid fever and cholera, their occurrence is influenced by personal infection rather than by any definite vices of sanitation. Measles and smallpox are the most contagious of all diseases; a momentary exposure of an unprotected person to the infection of smallpox or measles suffices for such individual to contract the disease. According to the Registrar-General's Reports, during the same period in England that smallpox mortality has declined 72 per cent., the mortality from measles has fallen only 9 per cent. Furthermore, the death-rate from whooping-cough has declined but a little more than 1 per cent. (at present whooping-cough is the most fatal of all diseases in children under two years of age), and the diminution in the mortality of scarlet fever has become apparent

TABLE 6.—DEATHS FROM SMALLPOX IN LONDON

Year.	Smallpox Deaths.	Year.	Smallpox Deaths.
1629.....	72	1698.....	1,813
1630.....	40	1699.....	890
1631.....	58	1700.....	1,031
1632.....	531		
1633.....	72	1691-1700	11,028
1634.....	1,354		
1635.....	293	1701.....	1,099
1636*.....	127	1702.....	311
1647.....	139	1703.....	398
1648.....	401	1704.....	1,501
1649.....	1,190	1705.....	1,095
1650.....	184	1706.....	721
1651.....	525	1707.....	1,078
1652.....	1,279	1708.....	1,687
1653.....	139	1709.....	1,024
1654.....	832	1710.....	3,138
1655.....	1,294		
1656.....	823	1701-10	12,052
1657.....	835		
1658.....	409	1711.....	915
1659.....	1,523	1712.....	1,943
1660.....	354	1713.....	1,614
		1714.....	2,810
1661.....	1,246	1715.....	1,057
1662.....	768	1716.....	2,427
1663.....	411	1717.....	2,211
1664.....	1,233	1718.....	1,884
1665.....	655	1719.....	3,229
1666.....	38	1720.....	1,442
1667.....	1,196		
1668.....	1,987	1711-20	19,532
1669.....	951		
1670.....	1,465	1721.....	2,375
		1722.....	2,167
1661-70	9,950	1723.....	3,271
		1724.....	1,227
1671.....	696	1725.....	3,188
1672.....	1,116	1726.....	1,569
1673.....	853	1727.....	2,379
1674.....	2,507	1728.....	2,105
1675.....	997	1729.....	2,849
1676.....	359	1730.....	1,914
1677.....	1,678	1721-30	23,044
1678.....	1,798		
1679.....	1,967	1731.....	2,640
1680.....	689	1732.....	1,197
		1733.....	1,370
1671-80	12,660	1734.....	2,688
		1735.....	1,594
1681.....	2,982	1736.....	3,014
1682.....	1,408	1737.....	2,084
1683.....	2,096	1738.....	1,590
1684.....	1,560	1739.....	1,690
1685†.....	2,496	1740.....	2,725
1686.....	1,062		
1687.....	1,551	1731-40	20,592
1688.....	1,318		
1689.....	1,389	1741.....	1,977
1690.....	778	1742.....	1,429
		1743.....	2,029
1681-90	16,640	1744.....	1,633
		1745.....	1,206
1691.....	1,241	1746.....	3,236
1692.....	1,592	1747.....	1,380
1693.....	1,164	1748.....	1,789
1694.....	1,683	1749.....	2,625
1695.....	784	1750†.....	1,229
1696.....	196		
1697.....	634	1741-50	18,533

TABLE 6.—CONTINUED

Year.	Smallpox Deaths.	Year.	Smallpox Deaths.
1751.....	998	1777.....	2,567
1752.....	3,538	1778.....	1,425
1753.....	774	1779.....	2,493
1754.....	2,359	1780.....	871
1755.....	1,988		
1756.....	1,608	1771-80	20,923
1757.....	3,296	1781.....	3,500
1758.....	1,273	1782.....	636
1759.....	2,596	1783.....	1,550
1760.....	2,181	1784.....	1,759
		1785.....	1,999
1751-60	20,611	1786.....	1,210
1761.....	1,525	1787.....	2,418
1762.....	2,743	1788.....	1,101
1763.....	3,582	1789.....	2,077
1764.....	2,382	1790.....	1,617
1765.....	2,498		
1766.....	2,334	1781-90	17,867
1767.....	2,188	1791.....	1,747
1768.....	3,028	1792.....	1,568
1769.....	1,968	1793.....	2,382
1770.....	1,986	1794.....	1,913
		1795.....	1,040
1761-70	24,234	1796.....	3,548
1771.....	1,660	1797.....	522
1772.....	3,992	1798.....	2,237
1773.....	1,039	1799.....	1,111
1774.....	2,479	1800§.....	2,409
1775.....	2,669		
1776.....	1,728	1791-1800	18,477

* The records of smallpox deaths from 1636 to 1647 have been lost, but it is known that in 1641 an extensive epidemic of the disease prevailed.

† Population within the Bills of Mortality estimated to be in 1685, 530,000.

‡ Population in 1750 estimated to be 653,900.

§ Population of London, determined by census, in 1801 was 746,233.

TABLE 7.—DEATHS PER 10,000 MEN *

Prussian Army Cause.		French Garrison of Langres Cause.	
Smallpox	5.8	Smallpox	222.6
Dysentery	32.3	Dysentery	19.3
Typhoid	118.8	Typhoid	80.6

* Table taken from Lotz: Pocken und Vaccination, Basel, 1880; presented in evidence before the Royal Commission on Vaccination.

only within comparatively recent years. Again the improvement in sanitation and mode of living has only caused a reduction of the general death-rate of the country (England) of 9 per cent.

The lack of parallelism between the incidence and mortality of smallpox and of other diseases due to bad sanitation is illustrated in the comparison of the Prussian and French troops in the Franco-Prussian war contained in Table 7.

The Prussian army was greatly exposed to smallpox as a large part of it was invading France, where this disease was raging. It was known that vaccination was much more thoroughly carried out in the Prussian than in the French army.

Another noteworthy fact must not be forgotten, namely, that the decline in the death-rate from smallpox has been entirely limited to persons below the age of fifteen. It is evident, therefore, that the lives of an enormous number of children have been saved. It is most illogical to attempt to explain such an inequality in the decline of smallpox mortality on the grounds of improved sanitation. The percentage of mortality borne by children who are the subjects of measles, scarlet fever, and whooping-cough does not differ materially from what it was a century ago.

The true explanation of the decline of smallpox mortality in children is that successfully vaccinated infants are almost completely protected against smallpox throughout the first decade of their lives. After this period, the vaccinal protection commonly begins to wane.

The decline in smallpox was manifest in all countries where vaccination was extensively practiced, no matter what the status of sanitation was. The case of Glasgow is a good example: The population of Glasgow in 1831 was almost five times what it was in 1780. There was overcrowding in tenement houses, lack of isolation in hospitals and absence of disinfection: the general sanitary condition was considered to be worse than that of any large town in England. Yet with an increasing population, with sanitation growing worse, with measles and whooping-cough deaths multiplying, the mortality from smallpox was lessened 80 per cent., with nothing to account for the reduction save vaccination.¹⁰

ISOLATION PROPOSED AS A SUBSTITUTE FOR VACCINATION

The isolation of smallpox patients and general sanitary measures are urged by the antivaccinationists as substitutes for vaccination. The isolation of patients suffering from transmissible diseases of any kind is recognized by all sanitarians as a most important procedure. But to disregard vaccination and rely on isolation to combat an extensive epidemic of smallpox would

10. Jenner Number of Public Health, 1896.

be an act of folly which would not be long tolerated by any intelligent community.

Anyone with practical knowledge of smallpox knows that smallpox is often not recognized until many persons have been exposed to infection. Mild cases of smallpox commonly escape detection while the patient is abroad in the community. Moreover, it is impossible to diagnose smallpox before the eruption appears; during the several days preceding the outbreak of the eruption those persons in contact with the patient may receive the infection of the disease.

In regard to isolation, the Royal Commission on Vaccination says: "We can see nothing to warrant the conclusion that in this country vaccination might be safely abandoned and replaced by a system of isolation." The commission, of course, favored isolation as an auxiliary to vaccination.

Dr. Werner¹¹ refers to attempts to suppress smallpox by isolation in Germany before 1834.

Isolation was most rigidly enforced; the patients were removed to smallpox stations and special houses; even seals were placed on the door of the patients' rooms. The patients' clothes were disinfected or burnt, and themselves and their attendants kept under watch and ward. All to no purpose—the pest found a way through the closed doors till suppressed by vaccination without the cooperation of sanitary measures.

SMALLPOX IN THE VACCINATED AND UNVACCINATED

It is not claimed at the present day that a single vaccination will invariably protect against smallpox for life. In the endeavor of the opponents of vaccination to prove that vaccination does not protect against smallpox, statistics are frequently cited to show that a large number of vaccinated persons contract the disease. This is an argument on which the antivaccinationists are prone to lay great stress. The argument, however, is specious and merely demonstrates that a single vaccination does not, as a rule, confer life-long protection against smallpox. If provision is not made for the renewal of protection by revaccination at a later period, the subjects are only in a measure secured against smallpox. England and other countries have had for many years a compulsory vaccination law, but it has had reference only to vaccination in infancy. It has resulted in an

11. Werner: *Deutsch. med. Wchnschr.*, May 14, 1896.

enormous saving of child life, but it has failed to provide for the protection of adults after the vaccinal immunity has died out.

Germany is the only one of the great countries of the world that has had experience for a sufficient period of time with a compulsory vaccination and revaccination law properly enforced, and Germany has been for thirty-five years free of epidemics of smallpox, although the contiguous countries have suffered from epidemics of this disease.

THE CLAIMS FOR VACCINATION

It is easy to comprehend why a single vaccination may not be relied on for perpetual protection against smallpox. Smallpox itself is, in rare instances, followed by another attack later in life. Now if one attack of smallpox does not invariably protect against a second, how could we expect vaccination, which in reality represents a benign, non-contagious and attenuated smallpox, to accomplish this desired end?

1. *A successful vaccination protects the subject against smallpox for a period of time not mathematically determinable for the individual, but which averages seven to ten years.*

2. *The protection may be renewed by a second vaccination when the vaccinal immunity is exhausted. The revaccination restores the protection which lapse of time has diminished or abrogated.*

3. *Persons successfully vaccinated on two occasions are usually immune against smallpox for life.* There are exceptional instances, however, of unusually susceptible individuals in whom a third or fourth vaccination is required. These exceptions are comparable with those rare cases in which a person is susceptible to a second or third attack of smallpox.

4. *Persons vaccinated in infancy, who at some later period of life contract smallpox, have in the aggregate less severe and less frequently fatal attacks than unvaccinated persons.* The degree of favorable modification of the smallpox is in inverse proportion to the period of time elapsing between vaccination and the attack of smallpox. The statistics as to the mortality of smallpox in the vaccinated and the unvaccinated are later set forth.

5. *The beneficent effects of vaccination are most pronounced in those in whom the vaccine affection has run its most typical and perfect course, and who bear the best quality of vaccinal scars as attestation of the same. The mere production of a "sore arm" does not necessarily imply that the individual has been successfully vaccinated.*

STATISTICS OF SMALLPOX IN THE VACCINATED AND THE UNVACCINATED

The experience of one hundred years offers absolutely conclusive proof of a most pronounced difference in the mortality from smallpox in the vaccinated and the unvaccinated. Variations in the severity of different epidemics occur, but the comparison of the death-rate in the two classes always yields the same result.

TABLE 8.—DEATH-RATE FROM SMALLPOX AMONG VACCINATED AND UNVACCINATED IN VARIOUS COUNTRIES *

Places and Time of Observation.	Total No. of Cases Observed.	Death Rate per 100 Cases.	
		Among the Unvac- cinated.	Among the Vac- cinated.
France, 1816-1841	16,397	16.125	1
Quebec, 1819-1820	?	27	1.66
Philadelphia, 1825	140	60	0
Canton Vaud, 1825-1829	5,838	24	2.16
Verona, 1828-1829	909	46.66	5.66
Milan, 1830-1851	10,240	38.33	7.66
Breslau, 1831-1833	220	53.8	2.11
Württemberg, 1831-1835	1,442	27.33	7.1
Carniola, 1834-1835	442	16.25	4.4
Vienna Hospital, 1834.....	360	51.25	12.5
Carinthia, 1834-1835	1,626	14.5	0.5
Adriatic, 1835	1,002	15.2	2.8
Lower Austria, 1835.....	2,287	25.8	11.5
Bohemia, 1835-1855	15,640	29.8	5.16
Galicia, 1836	1,059	23.5	5.14
Dalmatia, 1836	723	19.66	8.25
London Smallpox Hospital, 1836- 1856	9,000	35	7
Vienna Hospital, 1837-1856.....	6,213	30	5
Kiel, 1852-1853	218	32	6
Württemberg (no date).....	6,258	38.9	3 1/2
Malta (no date).....	7,570	21.07	4.2
Epidemiological Society Returns (no date)	4,624	23	2.9

* Extract from papers prepared in 1857 by Sir John Simon, Medical Officer of the General Board of Health of England, and at that time laid before Parliament with reference to the History and Practice of Vaccination. Published in first Report of the Royal Commission on Vaccination, 1889, Appendix 1, p. 74.

The figures cited in Table 8 show that among thousands of cases of smallpox occurring in cities all over the

world the death-rate from smallpox has been from five to sixteen times greater among the unvaccinated than among the vaccinated.

In an epidemic of smallpox in Marseilles, in 1828, the unvaccinated had a mortality of 25 per cent., as compared with 0.5 per cent. among the vaccinated.

The British Royal Commission on Vaccination presents the following statistics of six recent epidemics—in Dewsberry, 1891-92; Warrington, 1892-93; Leicester, 1892-93; London, 1892-93; Gloucester, 1892-93, and Sheffield. A grand total of 11,065 attacks is collected. This number resulted in 1,283 deaths, or 11.5 per cent., divided as shown in Table 9.

TABLE 9.—DEATHS AMONG VACCINATED AND UNVACCINATED IN SIX RECENT EPIDEMICS

	Vaccinated.	Unvaccinated.
Cases	8,744	2,321
Deaths.....	461	822
Per cent	5.2	35.4

The death-rate is therefore seven times greater among the unvaccinated than among the vaccinated.

THE RESULTS OF VACCINATION IN GERMANY

The relative immunity from smallpox mortality in the German army in 1871, as compared with that of the French army and of the civil population of Germany, led the German government to pass, in April, 1874, a general compulsory vaccination and revaccination law. The law requires the vaccination of all infants before the expiration of the first year of life, with revaccination at the age of 13.

Since the law of 1874 went into effect in Germany there have been no epidemics of smallpox in that country. The smallpox is frequently introduced by foreigners, particularly on the frontier, but the disease can find no foothold. In 1899 there occurred in the German empire, among 54,000,000 people, only 28 deaths from smallpox; these occurred in twenty-one different districts, the largest number in any one district being three. Not a death from smallpox occurred in a large town.

In 1897 there were but five deaths from smallpox in the entire German empire (54,000,000 population).

Furthermore, for a period of thirteen years, in a population comprising two-fifths of the total inhabitants of

TABLE 10.—DEATHS FROM SMALLPOX IN COUNTRIES WITH COMPELSSORY VACCINATION AND THOSE WITHOUT COMPULSORY VACCINATION

	Population.	Smallpox Deaths.			Average Per Million of Population.
		1886.	1887.	1888.	
Sweden*	4,746,465	1	5	9	2
Ireland*	4,808,728	2	14	3	1
Scotland*	4,013,029	24	17	0	5
Germany*	47,923,735	197	168	112	6
England*	28,247,151	275	50.5	1,026	12
Switzerland	2,922,430	182	14	17	3
Belgium	5,940,365	1,213	610	865	45.8
Russia	92,822,470	16,938	25,884	?	23
Austria	23,000,000	8,794	9,591	14,138	164
Italy	29,717,982	?	16,249	18,110	510
Spain	11,864,000	?	?	13,416	536
			14,378	8,472	11,425
				963	

* Compulsory vaccination.

Germany, there were only five instances of death from smallpox in successfully revaccinated persons.

Germany has taught the world how to utilize Jenner's great discovery so as to exterminate epidemics of smallpox.

The German Vaccination Committee of 1884, referring to the influence of the compulsory vaccination law, said:

The remarkable and persistent decline in Prussia since 1875 can be due only to the vaccination law of 1874, because all other conditions remain the same in the two other countries (i. e., Austria and Germany). The only difference is that in Prussia the revaccination of all school-children at the age of 12 years was made compulsory in 1874.

THE RESULTS OF VACCINATION REQUIREMENTS IN VARIOUS COUNTRIES

The Board of Health of Berlin has prepared tables comparing the number of deaths from smallpox occur-

TABLE 11.—THE FREQUENCY OF SMALLPOX IN EUROPEAN STATES BETWEEN 1893-1897 INCLUSIVE (FIVE YEARS)

Country.	Population.	Average Yearly Mortality in Every Million Population.	Actual Number Smallpox Deaths.	Year.
Germany	52,042,282	1.1	287	5
Denmark	793,356	0.5	2	5
Sweden	4,894,790	2.1	41	4
Norway	2,045,900	0.6	5	4
England and Wales....	30,389,524	20.2	3,066	5
Scotland	4,155,886	12.3	256	5
Ireland	4,580,555	9.9	226	5
Switzerland	3,032,901	5.1	78	5
Netherlands	4,797,249	38.7	929	5
Belgium	6,419,498	99.9	3,208	5
French States	8,253,079	90.2	3,721	5
Russian Empire, including Asiatic Russia	118,950,400	463.2	275,502	5
Austria	23,000,000	99.1	11,799	5
Italy	31,007,422	72.7	11,278	5
Spain	10,596,649	563.4	23,881	4
Hungary	18,234,916	134.3	12,241	5

ring between the years 1886 and 1889 in countries having compulsory vaccination and those without such provision.

But a glance is necessary to show the striking difference between the number of deaths in those countries having compulsory vaccination and those in which there is no such measure. The average deaths per million in the compulsory vaccination countries is eighty times less

than in the others. Furthermore, England is the least vaccinated of the compulsory countries and her death-rate is the highest among these.

The Imperial Board of Health of the German Empire gives the frequency of smallpox in various European countries between 1893 and 1897, inclusive, a period of five years.

Here, again, the countries which during this period have the most stringent vaccination laws suffer the least smallpox, namely, Germany, Denmark, Sweden and Norway.

In well-vaccinated Germany, but one person a year in every million of population died of smallpox.

In England and Wales, where vaccination is generally but not universally practiced, 20 persons per million died of smallpox each year.

It is, indeed, quite possible to know to what extent vaccination is practiced in the various countries by noting the mortality from smallpox.

The tables teach another lesson, namely, that without vaccination smallpox is still to be regarded as a dread scourge—as a great destroyer of human life. For in the five years from 1893 to 1897, in the sixteen countries mentioned, 346,520 lives were sacrificed to smallpox; of this number Russia lost 275,502. These figures are the more terrible when it is recognized that these lives might have been saved by the application of a prophylactic measure within the reach of all.

Thorough vaccination has practically banished smallpox from the huge German army. Kübler¹² says:

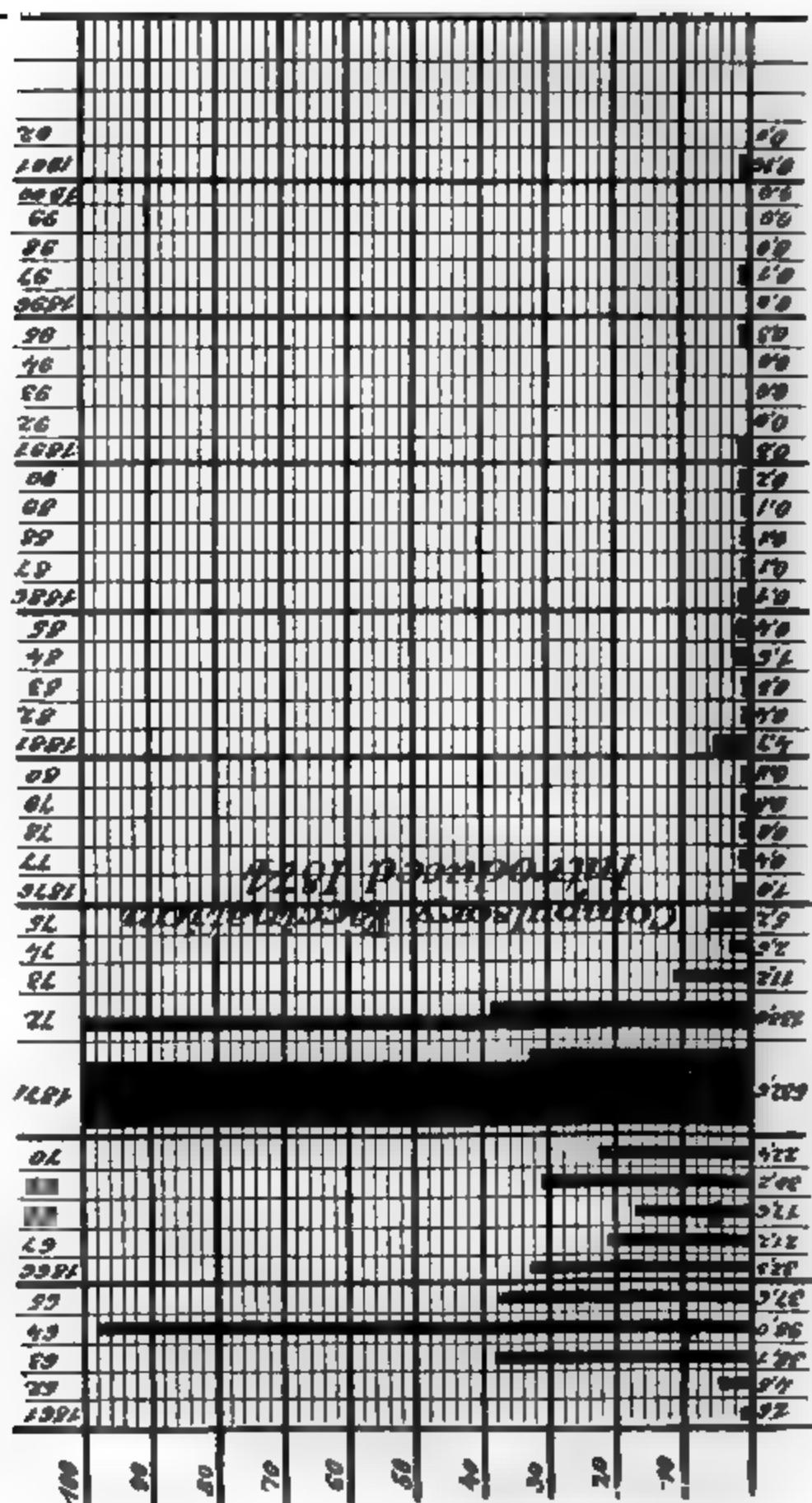
On only two occasions since the year 1874 (in 1884-85 and in 1889) has a death from smallpox occurred in the Prussian Army, and the first of these was in the person of a reservist who seven years before had been twice unsuccessfully vaccinated.

VACCINATION IN THE PHILIPPINE ISLANDS

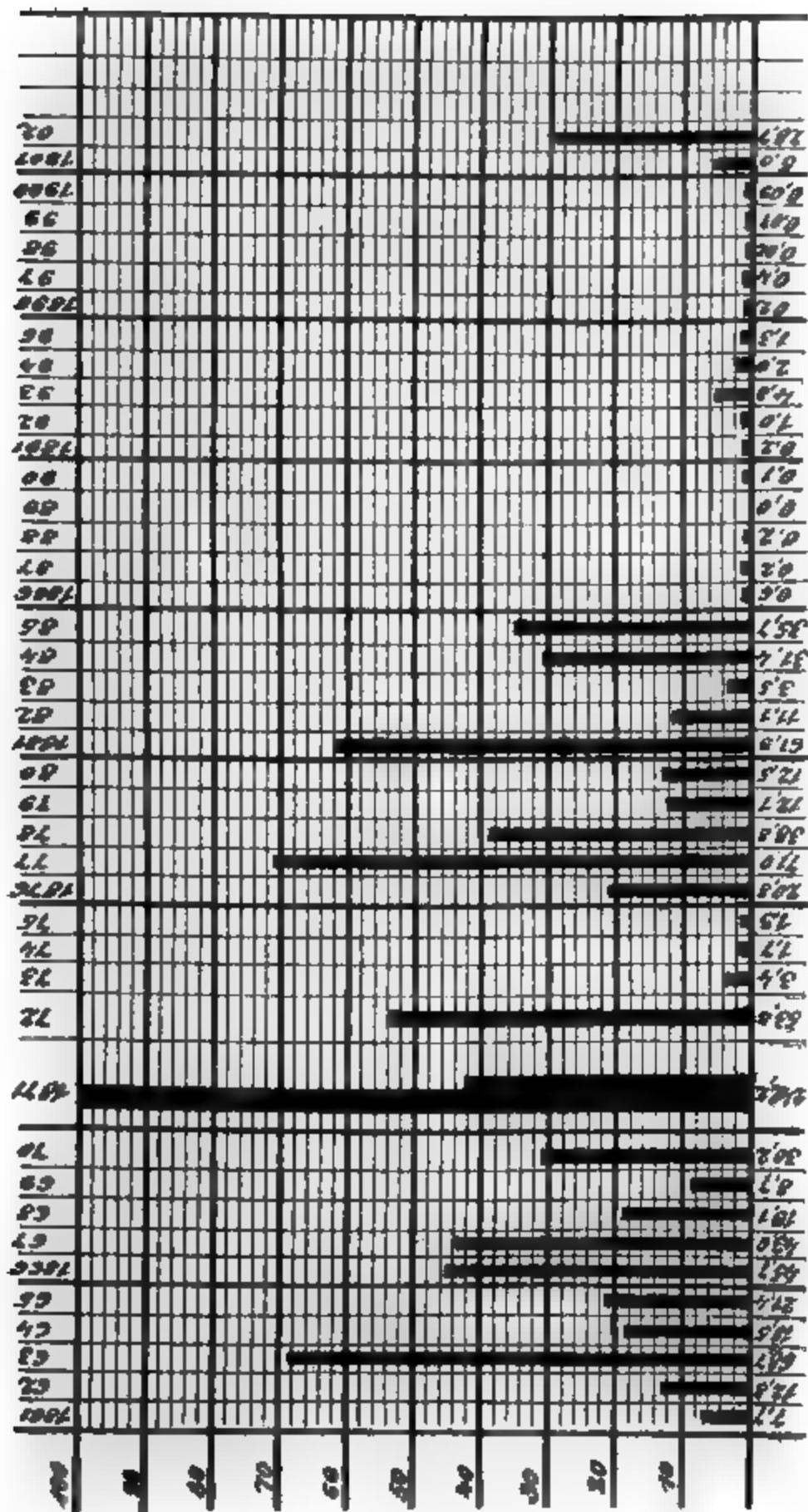
Of particular interest is the recent achievement of the United States sanitary authorities in stamping out smallpox in the Philippine Islands. In 1905 and 1906 the enormous number of 3,094,635 vaccinations were performed. Dr. Victor G. Heiser, Director of Health of the Islands, in the Report of the Bureau of Health (June 30, 1907), states:

12. Kübler: Geschichte der Pocken und der Impfung, 1901, p. 383.

BERLIN.—Smallpox Mortality Per 100,000 of Population.

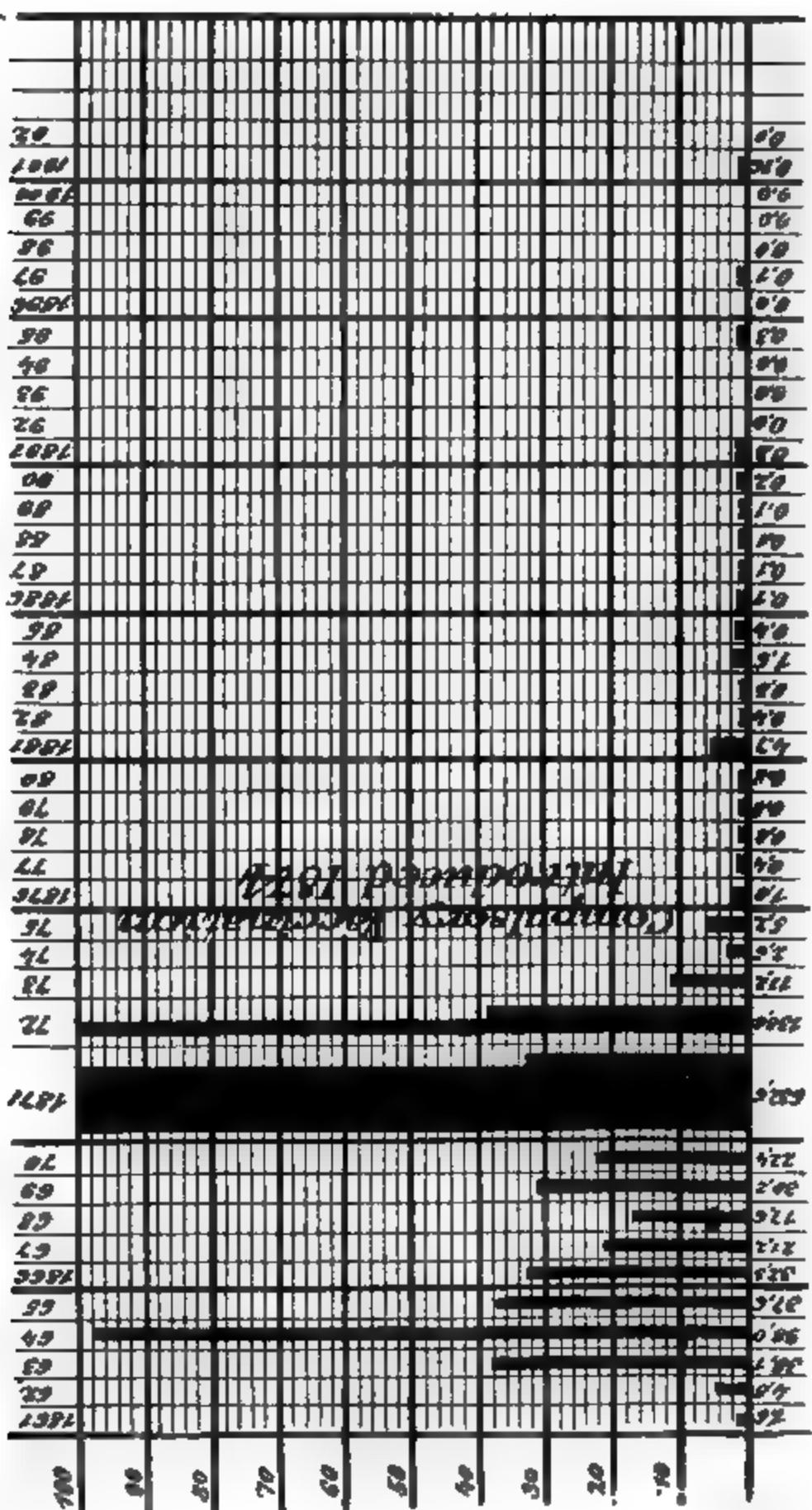


LONDON.—Smallpox Mortality Per 100,000 of Population.

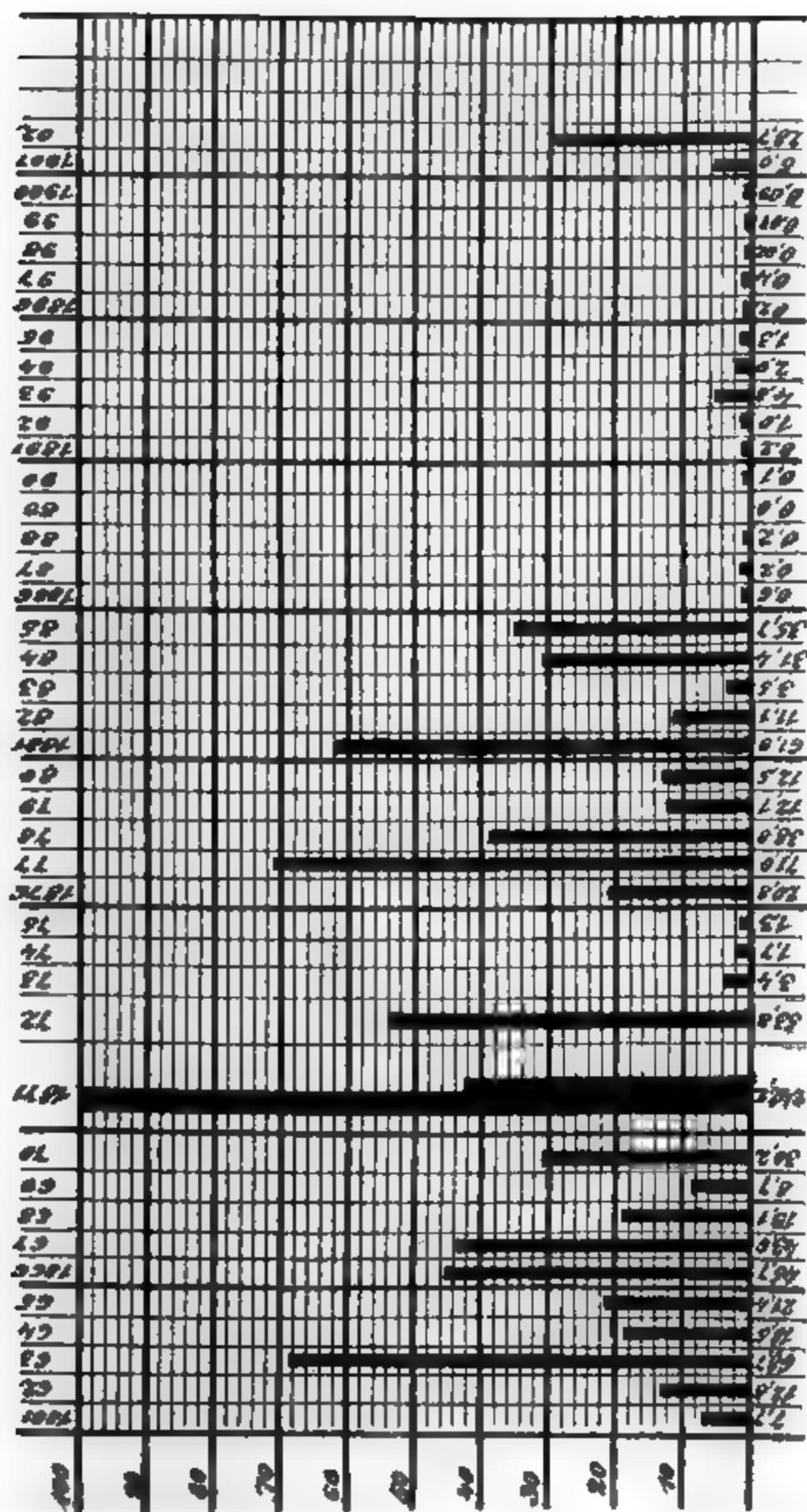


CHARTS 1 AND 2 (BERLIN AND LONDON). Comparison of mortality from smallpox per 100,000 of population.
Since 1874, Germany has a well-enforced compulsory vaccination and revaccination law, while England has merely
compulsory vaccination in infancy not generally enforced
(This chart and the others in this article are part of a series published by the German government in 1904.)

BERLIN.—Smallpox Mortality Per 100,000 of Population.

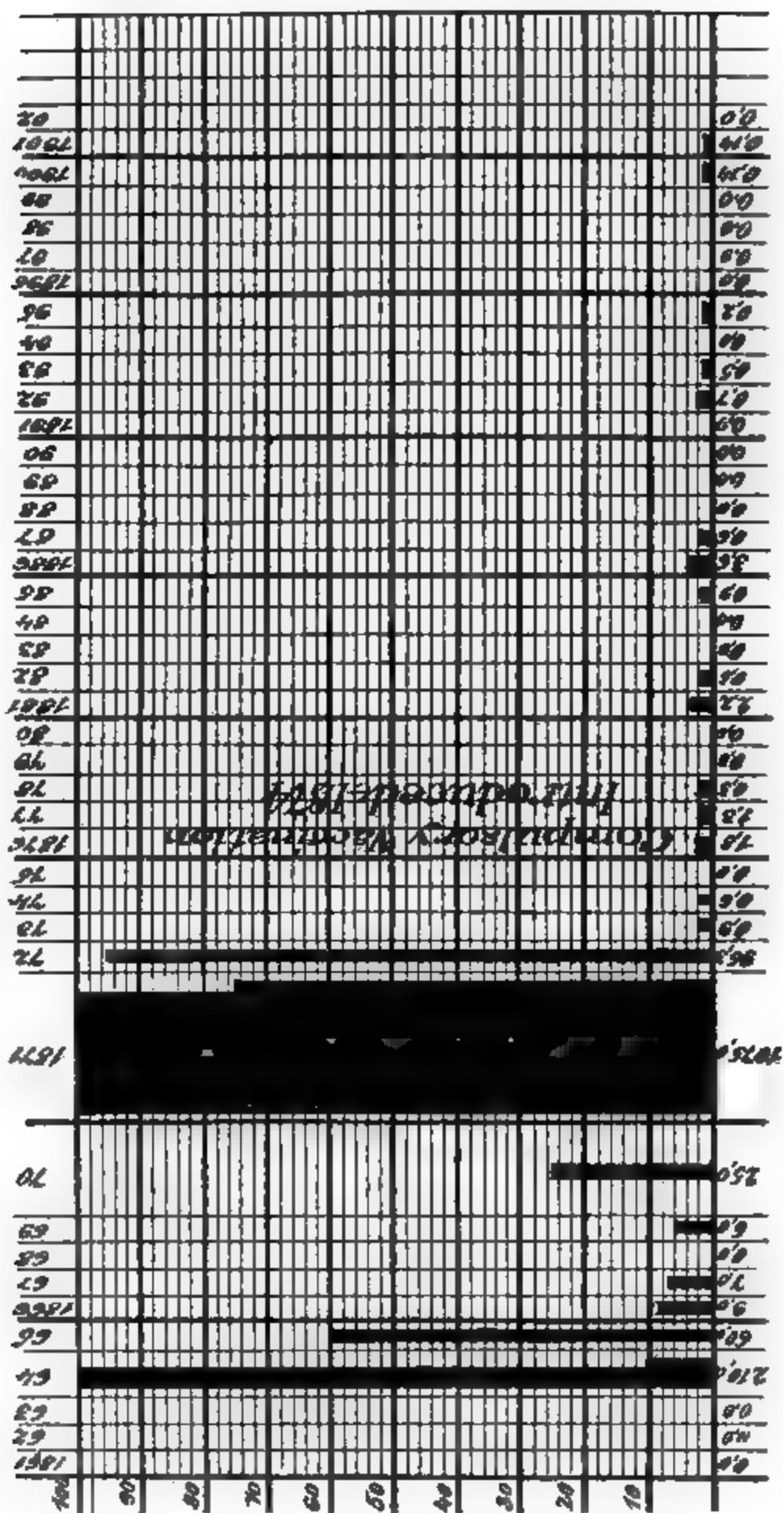


LONDON.—Smallpox Mortality Per 100,000 of Population.

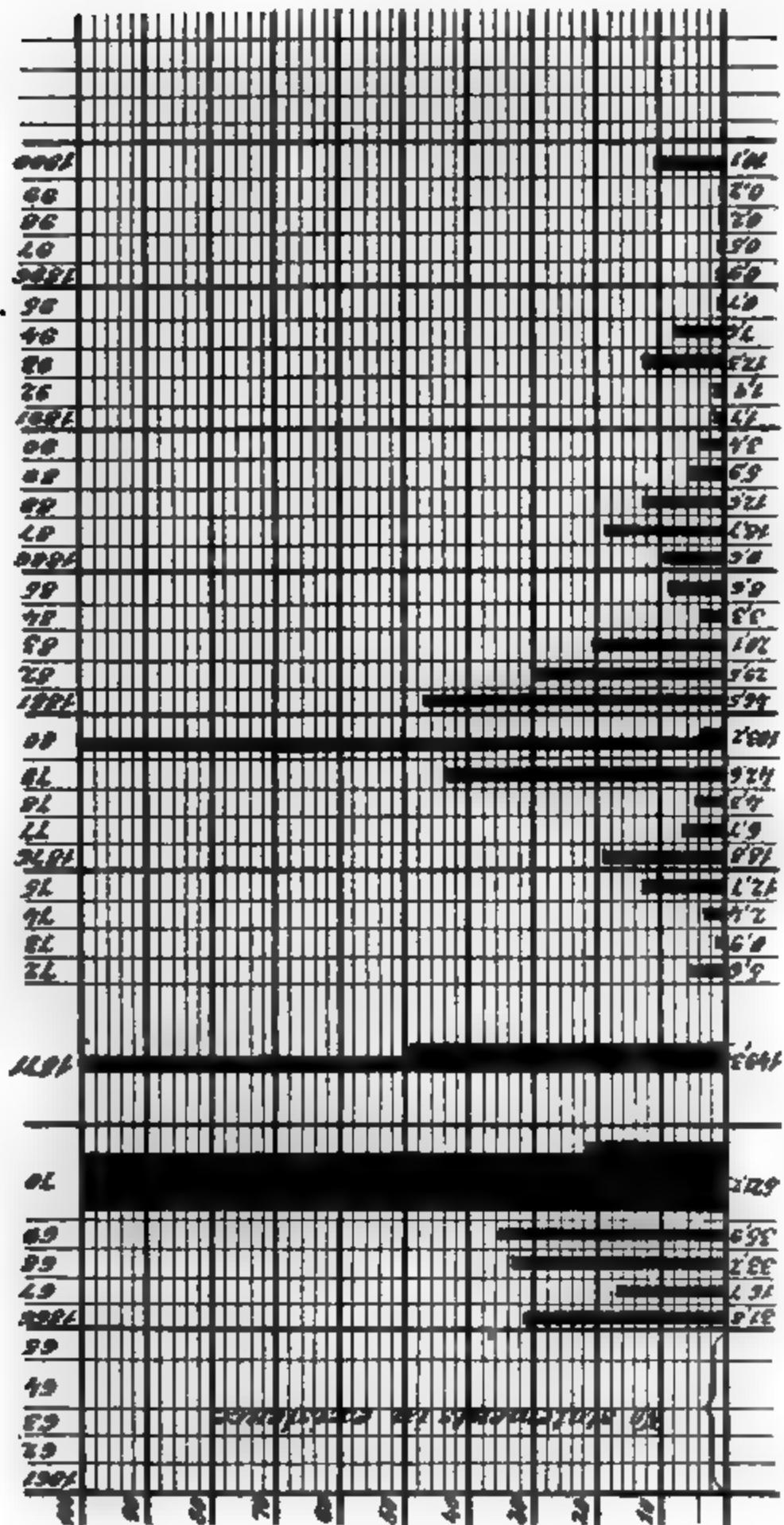


CHARTS 1 AND 2 (BERLIN AND LONDON).—Comparison of mortality from smallpox per 100,000 of population. Since 1874, Germany has a well-enforced compulsory vaccination and revaccination law, while England has merely compulsory vaccination in infancy not generally enforced. (This chart and the others in this article are part of a series published by the German government in 1904.)

HAMBURG.—Smallpox Mortality Per 100,000 of Population.



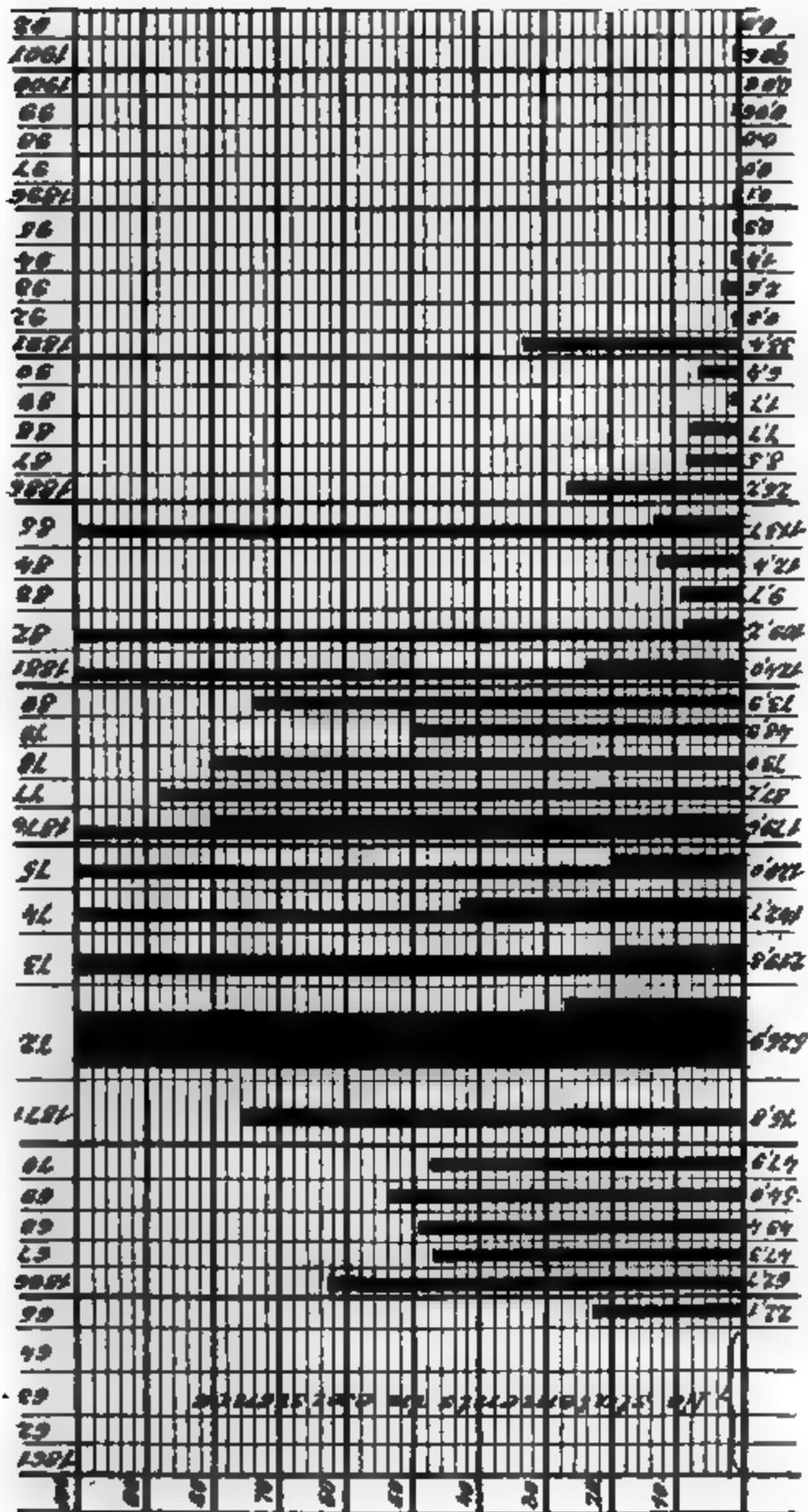
PARIS.—Smallpox Mortality Per 100,000 of Population.



CHARTS 3 AND 4 (HAMBURG AND PARIS)—Comparison of mortality from smallpox per 100,000 of population. In Hamburg no compulsory vaccination before 1874; since then compulsory vaccination and revaccination. In Paris no compulsory vaccination.

BRESLAU.—Smallpox Mortality Per 100,000 of Population.

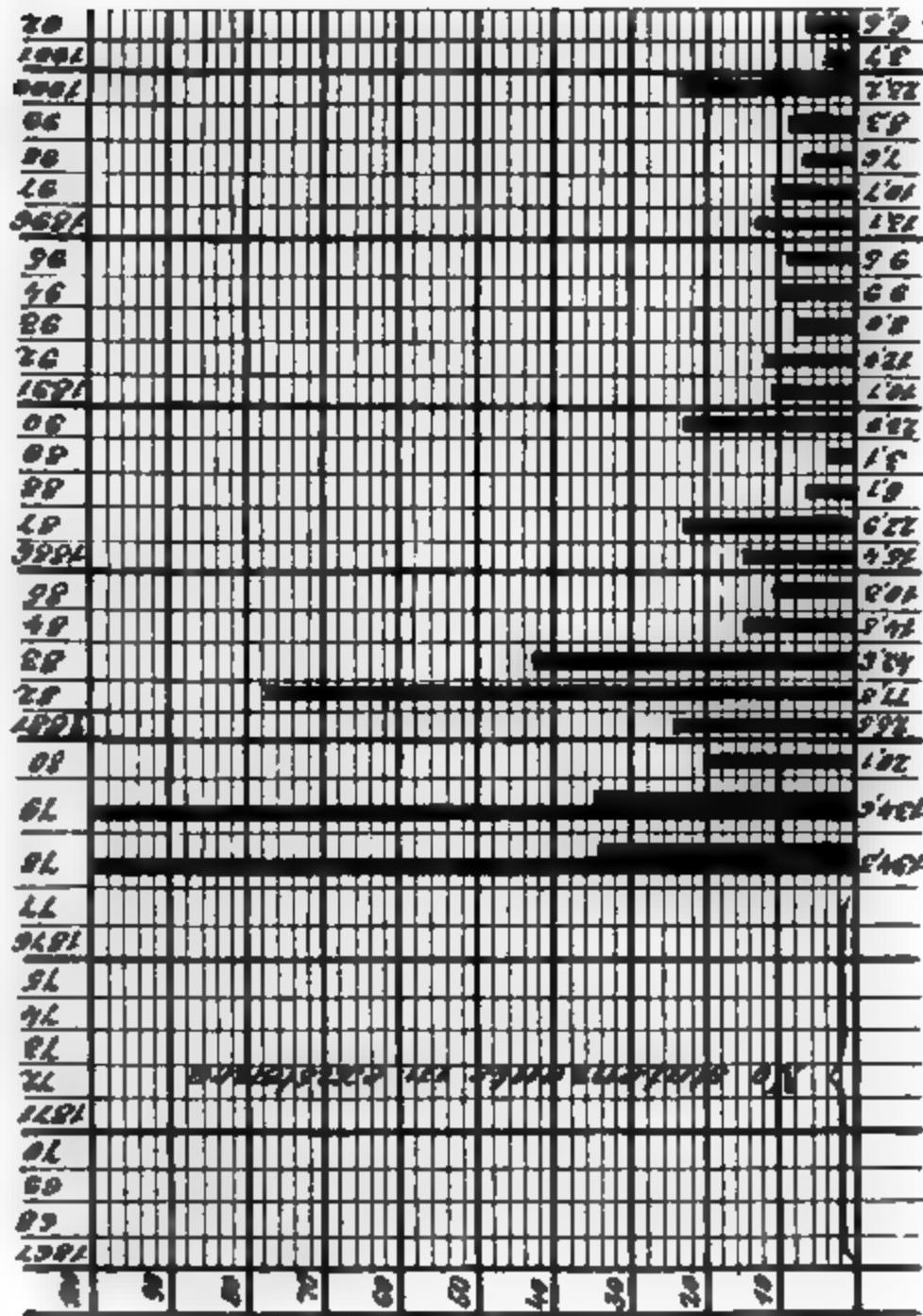
VIENNA.—Smallpox Mortality Per 100,000 of Population.



MUNICH.—Smallpox Mortality Per 100,000 of Population.

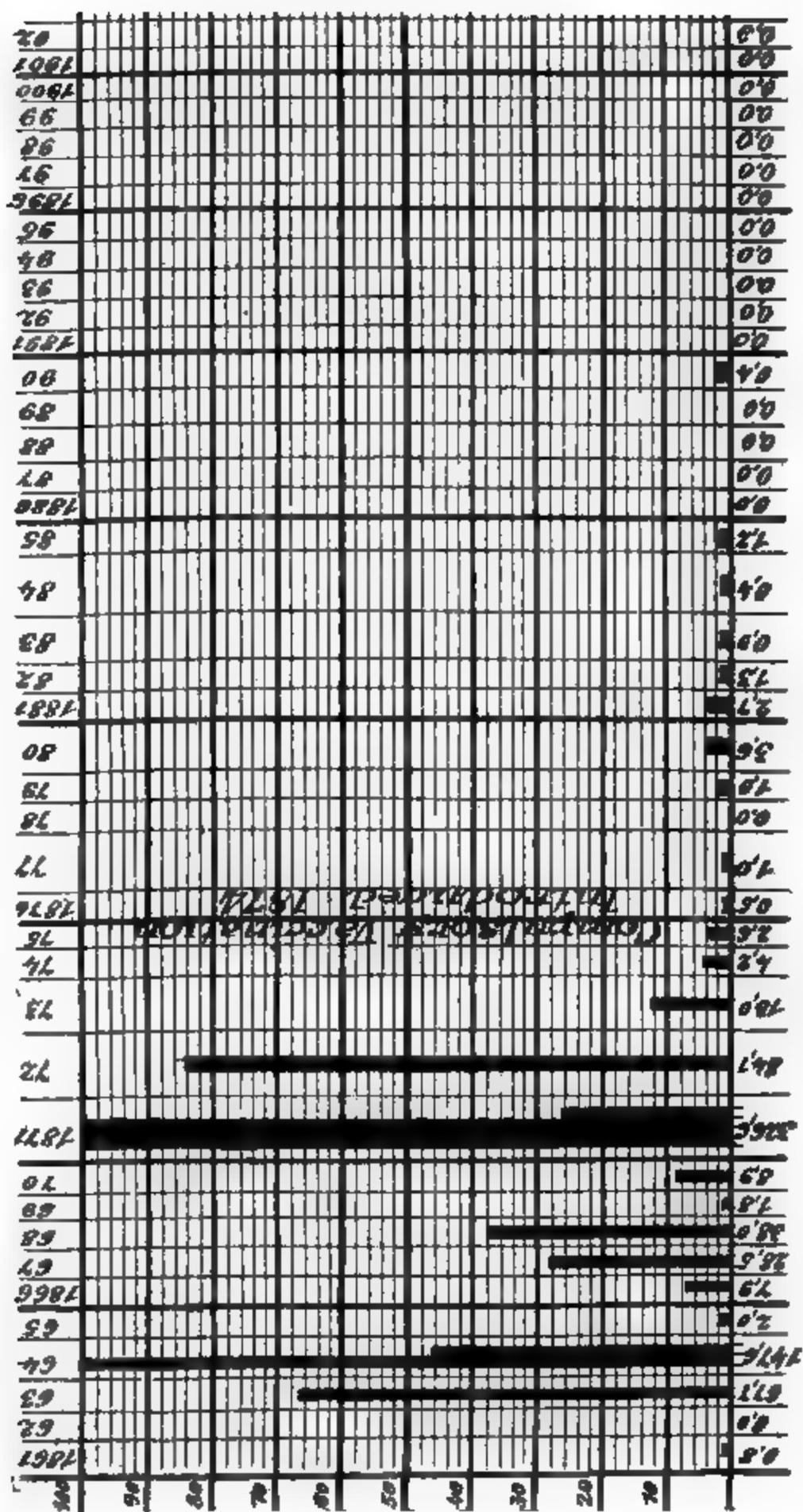
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ST. PETERSBURG.—Smallpox Mortality² Per 100,000 of Population.

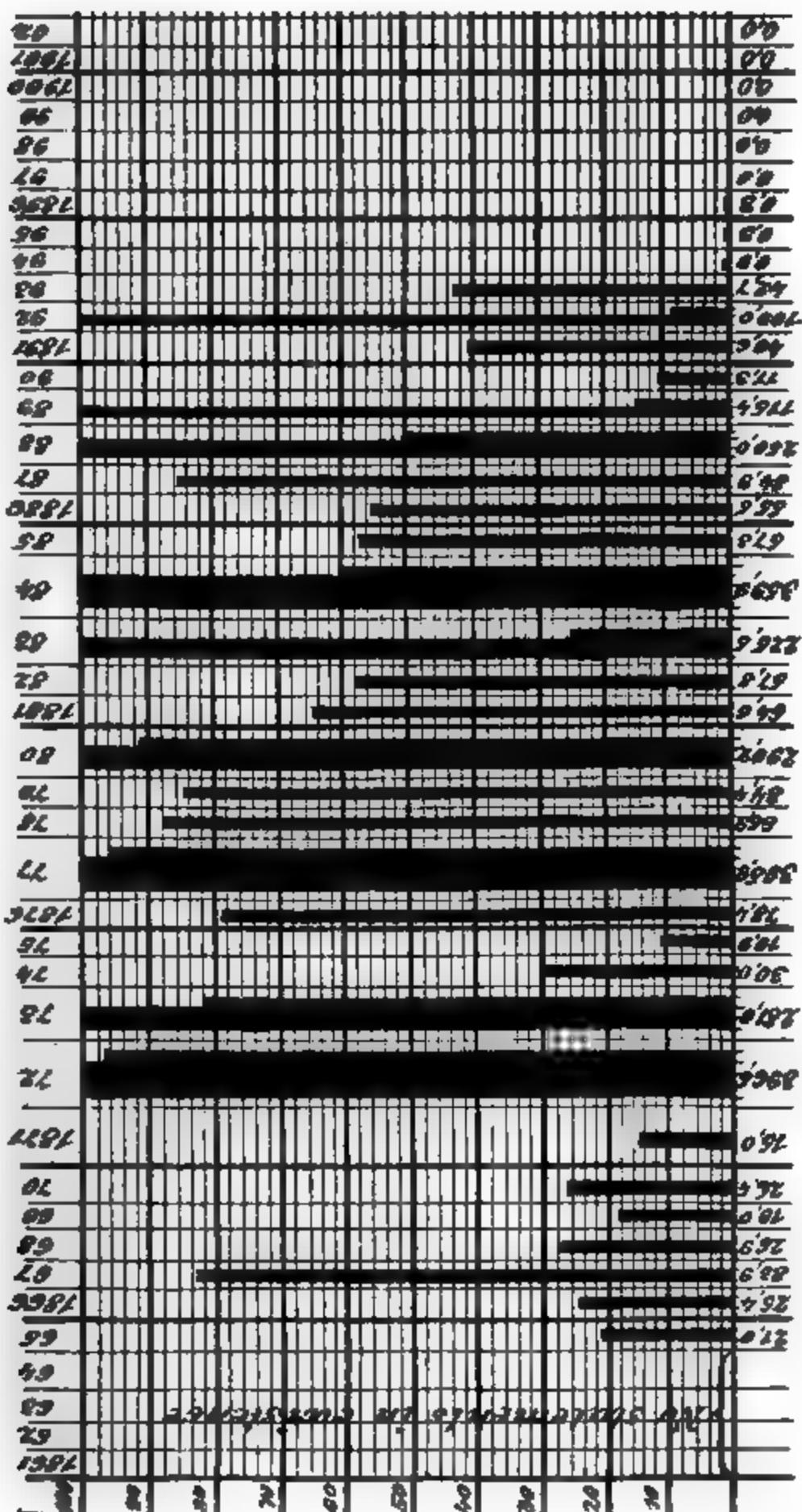


CHARTS 7 AND 8 (MUNICH AND ST. PETERSBURG).—Comparison of mortality from smallpox per 100,000 of population. In Munich before 1874, vaccination once for all; since then compulsory vaccination and revaccination. In St. Petersburg no compulsory vaccination.

DRESDEN.—Smallpox Mortality Per 100,000 of Population.

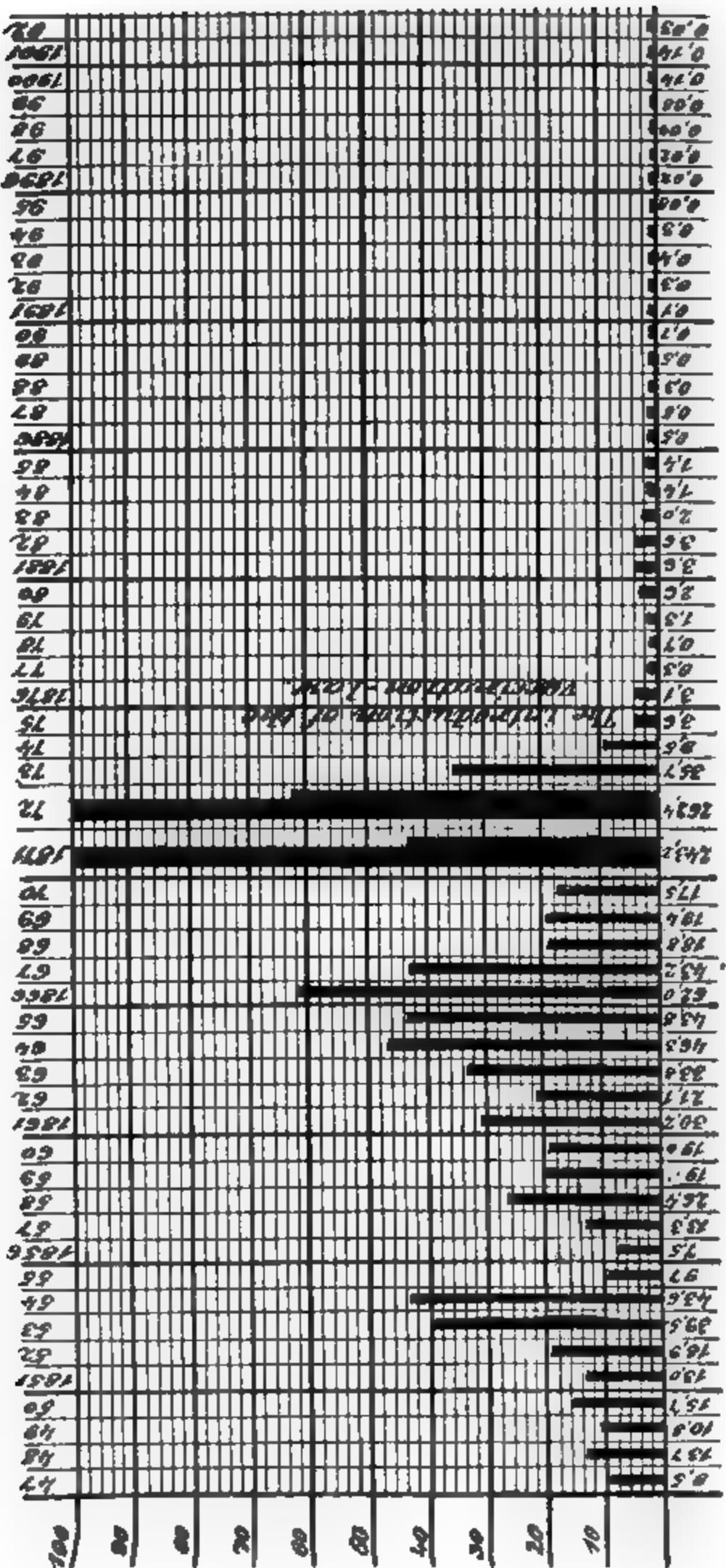


PRAGUE.—Smallpox Mortality Per 100,000 of Population.

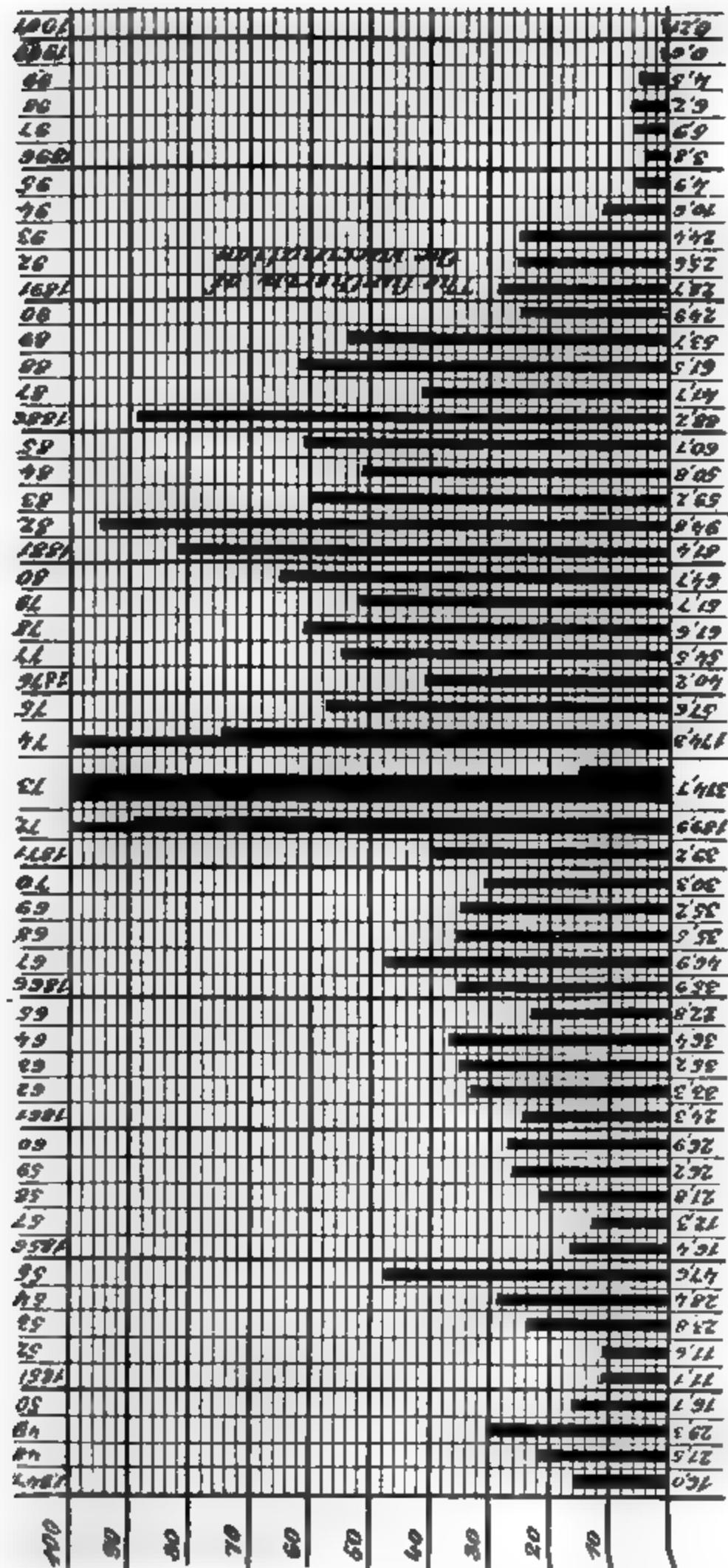


CHARTS 9 AND 10 (DRESDEN AND PRAGUE).—Comparison of mortality from smallpox per 100,000 of population. In Dresden no compulsory vaccination before 1874; since then compulsory vaccination and revaccination. In Prague no compulsory vaccination.

PRUSSIA.—Smallpox Mortality Per 100,000 of Population.



AUSTRIA.—Smallpox Mortality Per 100,000 of Population.



CHARTS 11 AND 12 (PRUSSIA AND AUSTRIA).—Comparison of mortality from smallpox during the years 1810-1902. There was very little difference in the number of deaths from the disease in the two countries as long as compulsory vaccination had not been introduced; since the enactment of the German vaccination law in Prussia, however, the mortality there has sunk to a previously unknown figure, whereas it has remained stationary and at the same high rate in Austria for many years. Up to 1880 the mortality from smallpox in the latter country was on an average greater than it was before the epidemic in 1872, and it is only since 1890 that favorable conditions have again prevailed, although the losses from smallpox have remained greater during recent years than in Prussia.

In the provinces of Cavite, Batangas, Cebu, Bataan, La Union, Rizal and La Laguna, where heretofore there have been more than 6,000 deaths annually from smallpox, it is satisfactory to report, since the completion of vaccination in the aforesaid provinces more than a year ago, not a single death from smallpox has been reported.

SMALLPOX EVER PRESENT IN PERSIA BECAUSE OF NEGLECT OF VACCINATION

A letter received by the Marquis of Salisbury from Dr. T. F. Odling, Medical Officer to the Indian Government Telegraphs, dated from Teheran, May 14, 1891, reads in part as follows:¹³

Vaccination is not compulsory in Persia and, except amongst the better class of people in large towns, it is not generally carried out; inoculation is still to a large extent the custom in the districts. . . . Smallpox is endemic and the large majority of children suffer from this disease at an early age. The deaths caused by smallpox are considerable, and the permanent injury in addition to the disfigurement caused by pitting inflicted on those who recover is very great, the loss of one eye or serious defect of vision being the most common.

TERRIBLE SLAUGHTER OF GUATEMALAN INDIANS BY SMALLPOX IN 1890

The decimating effects of smallpox in communities where vaccination is neglected may be further exemplified by reference to an epidemic in Guatemala in 1890-91. In an official dispatch, dated March 14, 1891, of Mr. Audley Gosling to the Marquis of Salisbury, the following is stated:¹⁴

I regret that the epidemic of smallpox which has raged here during the past fifteen months is still swelling the death-rate of this republic.

It is computed that since the first of January, 1890, no less than 112,000 deaths have occurred from this terrible scourge. The epidemic has been chiefly confined to the Indian population. . . .

Mr. Gosling encloses a letter from Dr. Q. H. Arton, practicing in Guatemala, who writes:

The natives have a strong prejudice to vaccination, simply because it involves the use of a lancet or other instrument, and not from any dread of the process *per se*. . . . So pig-headed are they, however, that although they have proofs given

13. Extract from evidence presented before the Royal Commission on Vaccination, Appendix No. 15, p. 756.

14. Extract from evidence presented before the Royal Commission on Vaccination, Appendix No. 15, p. 765.

them of the power to stop the epidemic in villages in which it is rampant, yet they will sooner attribute any cessation of the disease to the procession of some saint, and this belief is kept up by their so-called spiritual guides, who are in many cases equally ignorant with their flocks.

IMMUNITY OF VACCINATED PHYSICIANS, NURSES AND ATTENDANTS IN SMALLPOX HOSPITALS

If it can be demonstrated that physicians, nurses and attendants in smallpox hospitals can be perfectly protected by vaccination, then this must be regarded as a crucial test of its protective influence; for if these persons, living in the same atmosphere with scores or hundreds of smallpox patients, breathing their very exhalations, are enabled to escape the infection, it certainly should be possible for others much less exposed to acquire similar immunity.

Experience shows that physicians, nurses and attendants, if recently successfully vaccinated or revaccinated, may live in smallpox hospitals in perfect safety. Dr. Marson, physician to the Smallpox Hospital of London for many years, giving evidence in 1871, stated that during the preceding thirty-five years no nurse or servant at the hospital had been attacked with smallpox. Dr. Marson took the precaution of revaccinating all attendants before permitting them to go on duty. Dr. Collie, whose experience is also large, says: "During the epidemic of 1871, out of one hundred smallpox attendants at Homerton (England) all but two were revaccinated, and these two took smallpox." Dr. T. F. Ricketts, medical superintendent of the smallpox hospital ships on the Thames, states that out of 1,201 persons in attendance on board the smallpox ships, only six contracted the disease, all of them recovering. None of these six persons had been successfully revaccinated before going on duty. According to Dr. Hill, of Birmingham (England), during the epidemic of 1893, over one hundred persons were employed at the City Smallpox Hospital, all of whom had been recently revaccinated; not one of them contracted smallpox.

Dr. William M. Welch, of Philadelphia, states that in the Municipal Hospital of Philadelphia during a period of thirty-four years, in which time almost 10,000 cases of smallpox were treated, there was no instance of a physician, nurse or attendant who had been successfully



Fig. 1.—Two children in the Municipal Hospital of Philadelphia in 1903, one unvaccinated and the other vaccinated on the day of admission; the crust is still seen on the leg. This child remained in the hospital with its mother, who was suffering from smallpox for three weeks and was discharged perfectly well. The unvaccinated child, admitted with smallpox, died. (From "Acute Contagious Diseases," Welch and Schamberg.)



Fig. 2.—Three members of a family brought to the Municipal Hospital of Philadelphia with the mother, who was suffering from smallpox. The child in the center was unvaccinated; the other two had been vaccinated one year before as they were being prepared for kindergarten. These two children remained in the smallpox wards several weeks and left the hospital perfectly well (From "Acute Contagious Diseases," Welch and Schanberg.)



Fig. 3.—Two sisters, suffering from smallpox. The one on the right, aged 14, was successfully vaccinated in infancy, but not since. She contracted a mild smallpox, was never very ill and recovered without any scarring. The vaccinal scar is seen on the left arm. The girl on the left, aged 18, was never vaccinated. She developed a severe smallpox, which threatened her life and vision, but finally recovered although badly disfigured. Treated in the Municipal Hospital of Philadelphia in 1902. (From "Acute Contagious Diseases," Welch and Schamberg.)

vaccinated or revaccinated prior to going on duty contracting the disease.

EXPERIENCE OF THE MUNICIPAL HOSPITAL OF PHILADELPHIA IN THE EPIDEMIC OF 1901-1904

During this period over 3,500 cases of smallpox were received at the hospital. Not one patient, recently successfully vaccinated, was admitted to the hospital with smallpox. During the period of the outbreak of smallpox in Philadelphia, it is estimated that about 500,000



Fig. 4.—A normal appearance on the seventh day of vaccination
Compare the picture with that of smallpox.

persons were vaccinated—approximately a third of the population. If vaccination confers no protection against smallpox, it is reasonable to suppose that some of these persons would have contracted the disease and been brought to the hospital. (About 80 per cent. of all the cases in the city were sent to the hospital.) But no such patient could be found among over 3,500 admissions.

In order to provide accommodations in the Municipal Hospital for the unusually large number of cases of smallpox, which was rapidly increasing, it was necessary to erect additional buildings as well as enlarge those already in use. On this work from fifty to sixty men were employed, and, as they were required to come constantly into close proximity to the patients, they were all requested to come to the administration building and be vaccinated. This request was complied with by all except two, and these two took the smallpox. They were the only ones that were stricken by the disease.



Fig. 5.—Destruction of the eyeball from smallpox; it was necessary later to remove the eye.

Later it was found necessary to enlarge some of the buildings still further, and other workmen were employed. Two of them, for some reason which was never learned, neglected to get vaccinated before commencing the work, and they both took the smallpox.

The medical schools of Philadelphia had the privilege of sending their more advanced students to the Municipal Hospital for clinical instruction in the various contagious and infectious diseases therein treated. From 1901 to 1904 between 900 and 1,000 students visited the

smallpox pavilions and spent one or two hours among scores of virulent smallpox cases. One of the requirements was that each student had to show evidence of protection, either by having been recently successfully vaccinated or by not responding to vaccination after two or three careful trials. Of the entire number but one contracted smallpox, and it was subsequently found that not only had he never been successfully vaccinated, but that he came from an antivaccination family and was opposed to this prophylactic measure.

During the epidemic of 1901-1904 about 200 persons, including physicians, nurses, ward-maids, cooks, laundresses, and the like, were employed in the smallpox department, and not one contracted the disease; all, of course, had been vaccinated or revaccinated before going on duty.

Dr. William M. Welch, of Philadelphia, says: "In every epidemic of smallpox that has occurred in Philadelphia within the past thirty years, instances have been observed of whole families being removed to the hospital because of an outbreak of the disease in these families. In such instances the unvaccinated children have suffered and often perished, while those who were vaccinated remained perfectly exempt, although living, eating and sleeping in the infected atmosphere for several weeks. But I have yet to see unvaccinated children escape the disease under similar conditions of exposure. Furthermore, I have more than once seen a vaccinated infant take the daily supply of nourishment from the breast of its mother who was suffering from smallpox, and the infant continue as free from smallpox as if the disease were one hundred miles away and the food derived from the most wholesome source. This is evidence of the prophylactic power of vaccination that does not appear in mortality reports nor in statistical records."¹⁵

PHYSICIANS AND NURSES NOT PROTECTED AGAINST OTHER CONTAGIOUS DISEASES

Physicians and nurses do not exhibit immunity toward other contagious diseases as they do with respect to smallpox. According to Ernest Hart, in 1893, of 2,484 persons employed in the Metropolitan Fever Hospital of London, 130 became infected and 2 died. Four assistant

15. Welch and Schamberg: *Acute Contagious Diseases, Philadelphia, 1905.*

medical officers, 10 nurses, 43 assistant nurses, and 16 maid servants were attacked by scarlet fever. Two assistant medical officers, 6 nurses, and 15 assistant nurses contracted diphtheria.

While the deaths from smallpox of physicians (who constitute a class particularly well vaccinated) are but 13 per million, in England, the deaths of the general population are 73 per million. In scarlet fever, on the other hand, against which physicians have no special protection, the figures are reversed: 59 medical men per million die of scarlet fever, as against 16 per million of the general population.

ALLEGED DANGERS OF VACCINATION

Every human act is accompanied by some measure of danger. When one rides in an elevator, in a railroad car, or even promenades on the sidewalk, he takes a certain definite risk which can be mathematically calculated. While in the aggregate the number of accidents and deaths from each of these causes may be considerable, yet the individual risk is so small that it may be disregarded. It is the same with reference to vaccination.

Inasmuch as vaccination necessitates the production of an abrasion or wound, it is naturally liable to infections to which wounds from other causes are subject. Such a trivial accident as a pin-scratch or razor-cut has been known to lead to fatal termination. Most of the infections after vaccination occur in persons in whom regard for cleanliness is slight and in whom the subsequent care of the vaccination site is neglected.

If there is any class of men in the community who should be familiar with the accidents and complications of vaccination, it should certainly be the physicians. With this knowledge in their possession, medical men regard vaccination as so safe a procedure that they almost universally employ this measure on themselves, their wives, and their children. Indeed, physicians and their families constitute the best vaccinated class in the community. As has been said, English statistics show that only 13 medical men per million die of smallpox, against 73 per million of the general population, and the contrast is all the more striking in view of the fact that physicians are more exposed to smallpox than the average citizen.

Practically all of the accidents of vaccination are preventable by the selection of the proper virus and care of

the arm during and after vaccination. The United States Public Health and Marine-Hospital Service has supervision over the products of all vaccine establishments doing an interstate business and has the power to revoke the license of a firm placing impure virus on the market.

The dangers of vaccination have been enormously exaggerated by the opponents of this measure. In the Philippine Islands within the past few years there have been performed by the United States sanitary authorities 3,515,000 vaccinations without a single death or any serious postvaccinal infection.¹⁶ When we consider the thousands on thousands of vaccinations performed, even on the unclean and under unfavorable circumstances, and note how rare it is for any serious complication to develop, we are justified in concluding that the risk attending vaccination in any individual case is practically a negligible quantity. The danger connected with vaccination is infinitesimal compared with the peril of remaining unvaccinated.

UNANIMITY OF AUTHORITATIVE OPINION ON VACCINATION

It is difficult to understand that a medical procedure, which has stood the test of over one hundred years of experience and has satisfied the judgment of physicians and scientists, should encounter organized opposition outside of the profession. There has probably never been in the history of mankind a great discovery, the acceptance of which some men did not dispute. The great truth which Jenner gave to the world offers no exception to this statement. There are dissenters who do not believe in vaccination, but they are few in number and chiefly to be found outside of scientific circles. I know of no physician of eminence in this country who is not a believer in—nay, even an ardent advocate of vaccination. Every civilized government in the world has placed the stamp of its official sanction on vaccination, and practically all nations have made this procedure compulsory in their armies and navies. There is almost complete unanimity of sentiment among physicians concerning the efficacy of vaccination as a safeguard against smallpox.

^{16.} Strong, R. P.: Combating Tropical Diseases in the Philippines by Scientific Methods, THE JOURNAL A. M. A., Feb. 15, 1909, iii, 524.

The effort on the part of the lay opponents of vaccination to diffuse the idea that there is a pronounced difference of opinion among physicians as to the virtues of vaccination is absolutely without foundation in fact. It would be a difficult matter to find in this country five physicians in a hundred who are opposed to vaccination. Belief in the efficacy of vaccination has been repeatedly affirmed by the most noted scientific bodies in the world. Even as early as 1802 a committee of the British House of Commons investigated the subject and made a favorable report on the protective power of vaccination. In 1807 the Royal College of Physicians of London made a favorable report to the House of Commons. In 1804 a royal commission appointed in Denmark arrived unanimously at the conviction that vaccine virus was a preservative from smallpox. In 1856 John Simon, the medical officer of the London Board of Health, sent circular letters to 542 prominent members of the medical profession in the United Kingdom and Europe, requesting opinions as to the value of vaccination; 539 replies were received and there was absolute unanimity expressed as to the efficacy of vaccination as a protective measure against smallpox.

The most important opinion has been rendered by the British Royal Commission on Vaccination appointed by Queen Victoria in 1889. This commission, consisting of eminent members of Parliament, lawyers, scientists and physicians, and presided over by Lord Herschell, carried out an exhaustive investigation, lasting from 1889 to 1897. It held 136 meetings and examined 187 witnesses. The judgment of such a body as to the efficacy of vaccination should certainly be regarded as conclusive. In the final report signed by eleven of the thirteen members is found the following statement:

It is to be hoped that our report will stimulate belief in the efficacy of vaccination, that it will remove some misapprehension and reassure some who take an exaggerated view of the risks connected with the operation, as well as lead to a more ready enforcement of the law by local authorities.

To our knowledge, no scientific society has ever passed resolutions derogatory to vaccination; on the other hand, the highest scientific bodies throughout the world have repeatedly affirmed their belief in the virtues of vaccination.

On May 13, 1893, the Royal College of Surgeons of England, one of the most eminent bodies in Great

Britain, transmitted to the Royal Commission on Vaccination a set of resolutions bearing on vaccination, which reads in part as follows:¹⁷

We consider the evidence in favor of its life-saving power to be overwhelming, and we believe, from evidence equally strong, that the dangers incidental to the operation, when properly performed, are infinitesimal.

We should, therefore, regard as a national calamity any alteration in the law which now makes vaccination compulsory.

ANIMAL RESEARCH IN ITS RELATION TO VACCINATION AND SMALLPOX

The tradition concerning the protective influence of cowpox against smallpox appears to have been known to dairymen in England and Germany long before the days of Edward Jenner. Dairy servants whose hands were accidentally infected with cowpox while milking cows were alleged to be immune against the ever-present and fatal smallpox.

After assiduous investigation extending over many years, Jenner became convinced that there was truth in this strange belief. He carefully studied cowpox in the bovine and in the human species, and finally, after devoting much time and thought to the subject, inoculated material from the hand of a dairymaid on the arm of a young boy with complete success.

It remained for Jenner to crystallize the half-forgotten cowpox tradition into a scientific hypothesis, and then by painstaking study and experiment to prove its truth to the world.

The propositions set forth by Jenner may be briefly summarized as follows:

There is a disease affecting the heel of the horse which has been called by farriers "the grease."¹⁸ Dairy servants who come into contact both with horses and cows, accidentally transfer this affection from the horse to the cow in the process of milking the latter. An affection termed cowpox is thus produced on the udders and teats of the milch cows. Persons milking such cows commonly contract sores of a similar character on their hands. These persons are afterward immune against smallpox.

While Jenner's experimentation consisted largely in inoculating or rather vaccinating from one human sub-

17. Rep. Roy. Com. on Vaccination, Appendix No. 22, p. 778.

18. It is the prevailing belief nowadays that "the grease" or horsepox was not a necessary antecedent to cowpox; the two afflictions, in all probability, had a common ancestry.

ject to another, the material employed was primarily derived from the cow, which was, in its turn, accidentally inoculated from another cow or from the horse, usually through the mediation of the milker. An undesignated series of animal experiments was thus unconsciously carried out.

Jenner concerned himself also with some experimental research on cows in order to determine the stage at which the fluid from the equine affection was most likely to produce cowpox. In a footnote in his first publication in 1798 he says:

This [pus] I have often inserted into scratches made with a lancet on the sound nipples of cows, and have seen no other effects than simple inflammation.

The results of these experiments may have influenced the precept which, in his "golden rule of vaccination," Jenner later expressed, "never to take the virus from a vaccine pustule for the purpose of inoculation after the efflorescence is formed around it."

EXPERIMENTS BEARING ON THE RELATION OF VACCINATION TO SMALLPOX

With the best qualified and most persistent opponents of vaccination, such as Prof. E. M. Crookshank and Dr. Charles Creighton, the alleged lack of relationship between cowpox or vaccinia and smallpox constituted a vital argument in support of their views. It was maintained that, vaccinia and variola being two unrelated affections, the inoculation of the virus of the one could not possibly protect against the other. Had the basic premise been proved to be true, the conclusion would have had much scientific, though theoretical, weight. The force of this argument, however, has been annihilated within recent decades by the proof that a most intimate relationship exists between vaccinia and smallpox. Indeed, it has been demonstrated that the intensely contagious virus of smallpox can be transformed into the benign vaccine virus, the latter having the property of protecting against smallpox when inoculated into the human subject. Moreover, the affection produced by the vaccine virus, unlike that produced in the last century by inoculation of smallpox virus, results in a disorder which is non-contagious. This proof of the relation between vaccinia and smallpox has been brought about through animal experimentation carried

on through many years by scientific men in France, Switzerland, Germany and Great Britain. The British Royal Commission on Vaccination has thoroughly investigated these experiments and has reviewed the same in its voluminous report. While the experiments on the variolation of the bovine species have yielded results which exhibit marked variation, a considerable number of positive results have been attained in the hands of careful and trustworthy investigators at different times and in different countries. Fischer and Voigt in Germany, Haccius in Switzerland, Copeman in England, King in India, and others of late years have propagated cowpox virus by variolating heifers, producing thus what has been called variola-vaccine lymph. It has thus been conclusively demonstrated that smallpox may be converted into cowpox by successive inoculations of calves through several generations, the final inoculation yielding a pure vaccine virus. This virus when transferred to the human subject confers protection against smallpox.

It has taken almost a century of experimentation to prove the truth of the statement made by Jenner in his first publication, that smallpox and cowpox were modifications of the same disease. What a tribute to the intuitive discernment of this great man!

THE VALUE OF THE ABOVE EXPERIMENTS

The demonstration of the proof that vaccine virus may be developed from smallpox virus is of the greatest importance to mankind. Cases of spontaneous cowpox, from which most strains of vaccine lymph were originally derived, are excessively rare. In Württemberg, in 1825, a reward was offered for the discovery of cases of spontaneous cowpox. There is a reassuring sense of security, therefore, in the knowledge that in a case of the loss or attenuation of existing strains of lymph a fresh source may be obtained by variolation of calves. It has long been known that vaccine lymph may degenerate by too prolonged transmission through the human species. In years gone by the cry was often heard, "Back to the cow."

Again, in the event of a vaccine famine such as occurred in 1871-72, or in an extensive epidemic of smallpox in some inaccessible country where vaccine material could not be secured, the ability to convert the smallpox

virus into vaccine virus by inoculation of calves would offer the means of suppressing the epidemic.

Shakespeare might well have had vaccination in mind when he wrote:

Take thou some new infection to thine eye,
And the rank poison of the old will die.

ADVANTAGES OF BOVINE VIRUS OVER HUMANIZED VIRUS

1. About a quarter of a century ago it was the common practice to employ for vaccination the fluid or the dried crust from the vaccine lesion on a child's arm. While such vaccinations gave satisfactory results as regards protection against smallpox, they were attended with certain disadvantages which are obviated by the use of bovine lymph. The use of calf-propagated virus precludes the possibility of transmitting by vaccination diseases peculiar to the human species. One of the most weighty reasons that led to the adoption of animal vaccination and to its preference over arm-to-arm transmission was the recognition of the possibility of inducing syphilis by vaccine inoculation. To be sure, such accidents were so rare that thousands on thousands of physicians vaccinating throughout a lifetime failed to encounter any such unfortunate experience. Nevertheless, no matter how uncommon such a catastrophe might be, the remotest liability of such an occurrence constitutes a serious argument against the use of humanized virus. The opponents of vaccination bitterly attacked the procedure on the grounds just mentioned. The bovine species being totally insusceptible to syphilis, the use of lymph of calf origin is entirely devoid of the danger of transmitting syphilis. The weightiest argument of those who have antagonized vaccination is, therefore, nullified.

Erysipelas appears to be a much rarer complication since the general employment of animal virus. Many cases of vaccinal erysipelas were, in the past, doubtless due to secondary infection of the vesicle at the time that it was punctured to withdraw lymph for further vaccinations. The use of animal virus obviates the necessity of tapping the vaccine vesicle, thus rendering erysipelas from this cause practically non-existent. Many cases of erysipelas were also due to the use of crusts which had been unwisely selected or improperly preserved. Whatever the cause or causes may have been, actual experience shows an enormous reduction in the relative and total

incidence of this complication since calf virus has come into general use.

2. The virus of calves offers an almost inexhaustible supply of lymph, inasmuch as a much greater yield can be obtained from the calf than from the human subject, and, furthermore, the number of calves used can be multiplied according to existing needs. During extensive epidemics of smallpox when humanized virus was employed, the community was often placed in a most embarrassing and dangerous predicament owing to an insufficient supply of vaccine lymph. During the great pandemic of smallpox that spread over the entire globe in the early seventies a veritable vaccine famine existed in many countries. All kinds of sources were drawn on for virus, and much worthless lymph derived from spurious and irregular vaccinations was employed, with entirely unsatisfactory results.

3. Animal lymph appears to give a much larger percentage of successful revaccinations than long-humanized virus. Dr. Henry A. Martin says:

The number of those who in revaccination with old, long-humanized virus (not that of early human removes) experience vaccinal effect may be stated at the outside at 35 per cent. The number of those revaccinated with equal care and repetition with animal virus and virus of very early human removes, I affirm to be a fraction over 80 per cent.—a difference of 45 per cent.; and this 45 per cent. I firmly believe to represent approximately the number of those insensible to the enfeebled influence of long-humanized virus, but sensible to the intense contagion of variola just in the same degree as sensible to the intense power of bovine virus and that of the early human removes from it.

4. Vaccination with bovine lymph produces a vesicle which approaches more nearly the Jennerian prototype, and reaches, therefore, a greater degree of perfection than that produced by long-humanized virus.

The cowpox accidentally produced on the hands of dairymaids was believed by Jenner to confer lasting protection against smallpox. The bovine species appears to be the natural soil of the prophylactic pock, and the view has been maintained by many that calf virus or virus derived from an early human remove creates a more complete and permanent immunity.

It has been alleged by the opponents of vaccination that tuberculosis has been and is transmitted by the use of calf virus. The precautions which are adopted in

the propagation of vaccine virus make such an accident almost an impossibility. Even were this not the case, it is very doubtful whether an inoculation of virus contaminated with the tubercle bacillus would produce more than a local skin lesion which could be readily cured. The precautionary measures employed are, as has been said, an all-sufficient safeguard. The virus is obtained from very young calves, and it is pretty well established that calves are but rarely the subjects of tuberculosis. It is stated by Fürst,¹⁹ on the authority of Pfeiffer, that but one case of tuberculosis was found among 34,400 calves under four months of age. The statistics of the abattoirs of Augsburg and Munich corroborate the above figures; only one tuberculous calf was discovered at Augsburg among 22,230 slaughtered, and the percentage was much smaller at Munich.

Furthermore, in all well-regulated establishments for the propagation of vaccine virus, the calves are subjected for a number of days prior to vaccination to the tuberculin test; in the event that tuberculosis is shown to exist in the animal, it is, of course, not employed for vaccination. All calves used for vaccination are autopsied and carefully examined before the virus obtained from them is placed on the market. Finally, even though it were possible, despite these precautions for the tubercle bacillus to contaminate the lymph, it would perish if the virus were glycerinated. Nearly all of the vaccine lymph now employed is subjected to the process of glycerination. Copeman,²⁰ speaking of glycerinated lymph, says:

The tubercle bacillus is effectively destroyed even when large quantities of virulent cultures have been purposely added to the lymph.

EXPERIMENTAL RESEARCHES ON MONKEYS

A number of observers, including Zuelzer, Copeman, De Haan, Roger and Weil, Park, Ewing, and Councilman, McGrath and Brinckerhoff, have shown that it is possible to inoculate certain species of monkeys with smallpox, producing in them a mild affection similar to inoculated smallpox formerly induced for protective purposes in man. This inoculation protects the monkey

19. Fürst: *Die Pathologie der Schutz-Pocken-Impfung*, Berlin, 1896, paragraph 431, p. 112; quoted by Acland: *Allbutt's System of Medicine*.

20. Copeman: *Vaccination, Its Natural History and Pathology*, London, 1899, p. 181.

against subsequent successful inoculation and likewise against vaccination. In similar manner vaccination protects the monkey against inoculation smallpox. This is strong experimental proof of the protective power of vaccination. Monkeys are only slightly, if at all, susceptible to smallpox contracted in a natural way through the air. Professor Councilman, of Harvard University, and his associates allege that they have discovered the parasite which causes smallpox, the same organism somewhat modified being held to be present in the vaccine lesion. If this claim is confirmed and proved by further research, results of practical importance may be evolved from the labors of these investigators.

RECAPITULATION AND CONCLUSIONS

1. Vaccination, when properly and adequately employed, protects one against smallpox. Even those intimately exposed to the disease, as physicians and nurses in smallpox hospitals, may be made completely immune against smallpox by vaccination and revaccination.

2. Vaccination protects against smallpox in the same manner that one attack of the smallpox protects against a second attack. Vaccination has the special advantage in that the immunity which it confers against smallpox may be renewed when it becomes impaired or exhausted.

3. Vaccination in order to confer protection must be genuine: the mere production of a "sore arm" is of itself no proof that the subject has been successfully vaccinated. The vaccination must run a definite course before a protective substance is left in the body.

4. Smallpox may develop in vaccinated persons if they permit years to elapse without revaccination.

5. Vaccination and revaccination universally applied are capable of exterminating smallpox as an epidemic disease. The experience of Germany during the past thirty-five years proves this.

6. In isolated instances individuals in a generally well-vaccinated community may develop smallpox because their protection is imperfect as a result of the use of an inert virus or some other fault of technic. These cases, however, will never appreciably influence the prevalence of the disease in such a community.

7. Smallpox was an ever-present and terrible pestilence in the days before vaccination. In most civilized centers it is to-day a relatively rare disease. This change has been effected almost exclusively by vaccina-

tion. Epidemics of smallpox prevail from time to time when the spark of infection is introduced into the community and a sufficient amount of unvaccinated combustible material exists to lead to a general conflagration. In countries where vaccination is neglected, as in Persia, Asiatic Russia, etc., etc., smallpox is still a death-dealing scourge.

8. The foes of vaccination commonly refer to the infrequency of smallpox at the present day and to the remote liability of contracting the disease. They forget that the relative security which we now enjoy is the result of vaccination. This security can be made absolute or it can be largely destroyed according as vaccination and revaccination are generally employed or generally neglected.

9. The dangers connected with vaccination have been greatly exaggerated by the opponents of this measure. Vaccination causes an abrasion of the skin and in rare instances this wound, like other wounds may become infected, especially when neglected or maltreated. With the selection of a proper virus and care of the vaccination site during and after vaccination, the risk in any individual instance is an entirely negligible quantity. The risk connected with vaccination is infinitesimal compared with the peril of remaining unvaccinated.

THE RELATION OF ANIMAL RESEARCH TO OUR KNOWLEDGE OF SMALLPOX AND VACCINATION

1. Numerous experiments on calves have proved that smallpox virus may be converted into vaccine virus by transmission through several generations of the bovine species. This discovery not only establishes vaccination as a thoroughly scientific practice, but also provides for a new source of lymph in the event of the deterioration or loss of existing strains.

2. Experiments on calves have resulted in a method of calf vaccination which permits of the production of any needed quantity of virus. This renders unnecessary the use of humanized virus with the attendant disadvantages elsewhere referred to. The use of calves for the propagation of vaccine lymph constitutes the most important improvement in vaccination since its discovery over a hundred years ago.

ADDENDA

(Notes added to the second edition of this pamphlet, 1911.)

EFFECTS OF VACCINATION IN JAPAN

The opponents of vaccination in England and the United States have within recent years endeavored to prove that vaccination has been a failure in Japan. Taking the various vaccination laws in Japan as a guide, they have argued that the Japanese people were thoroughly and repeatedly vaccinated, and yet at times suffered considerable epidemics of smallpox. These results have been arrived at by antivaccinationists many thousands of miles distant from Japan, and were based solely on paper statistics. They point out that Japan, which is supposed to be a thoroughly vaccinated country, has had in the twenty years from 1889 to 1908, 171,500 cases of smallpox, and that in 1908 there were 18,139 cases. If the inhabitants of Japan were all thoroughly well vaccinated, these figures would seriously challenge the effectiveness of vaccination as a preventive measure against smallpox. There is, however, information at hand to show that a very large number of Japanese subjects have not been successfully vaccinated, and this information comes to us from an unimpeachable and authentic source. Dr. T. Amako, Director of the Municipal Hospital for Infectious Diseases, in Kobe, Japan, contributes an article entitled "A Study of the Variola Epidemic in Kobe" (*Archiv. f. Schiffs u. Tropen Hygiene*, 1909, xiii, page 409). He prefaces the statistics by stating that "fearful epidemics of smallpox have raged in Japan seventy times between the years 551 and 1884." He says that "vaccination was introduced into Japan in 1848, but was carried out very incompletely." In 1885 the first Imperial Vaccination Law was passed, and since then the former murderous epidemics of smallpox have been tremendously lessened through vaccination. In the year 1908, in the city of Kobe, with a population of 372,751, there were 4,184 cases of smallpox. Amako had an opportunity of observing 3,465 patients and of noting the relation between vaccination and smallpox in these cases; 1,607 patients, representing 46.4 per cent. of the entire number were vaccinated, and the remaining 1,856, or 53.5 per cent., were either unvaccinated or vaccinated unsuccessfully. Of the vaccinated cases, 116 died, representing a mortality of 7.2 per cent.; of the unvaccinated or unsuccessfully vaccinated cases, 851 died, representing a mortality of 45.8 per cent. It is thus seen that *the mortality among the unvaccinated cases was nearly seven times as great as among the vaccinated cases.*

There is certainly nothing in these figures which can possibly be construed to be unfavorable to vaccination. When by actual examination of the patients, an official finds over 50 per cent. of those suffering from smallpox to be unvaccinated or unsuccessfully vaccinated, there is no justification for the expectation that Japan should be free of epidemics of smallpox. It must, furthermore, be remembered that 18,000 cases of smallpox in a population of over 49,000,000 crowded together on a relatively small island, is not excessive when compared with the number of cases in other countries. According to the estimate of John W. Trask, of the U. S. Public Health and Marine-Hospital Service, there were probably more than 70,000 cases of smallpox in the United States in 1908. It is thus seen that the smallpox statistics of Japan as compared with the United States are much in favor of the former country.

But recently, an article entitled "Vaccination and Smallpox in Japan," has been published (THE JOURNAL A. M. A. March 25, 1911) by Kitasato, Director of the Institute for Research in Infectious Diseases, Tokio, Japan, and Physician to the Emperor of Japan. This eminent scientist says that vaccination was first introduced into Japan in 1849 by Monicke, a Dutch physician, and that the Japanese people were soon convinced of the marvelous effects of vaccination. He declares that the reasons for the occurrence of epidemics of smallpox in Japan are that:

1. Japan is surrounded by non-vaccinated countries whence contagion may flow in at any time.
2. The ignorant people frequently escape the provisions of the vaccination requirements.
3. A certain proportion of vaccinations performed are unsuccessful. At times 20 to 25 per cent. of the vaccinations fail to take, although since 1900 the number of unsuccessful primary vaccinations has been reduced to about 12 per cent.
4. Smallpox in Japan is usually of a highly virulent character, the mortality in the unvaccinated having reached at times 69.3 per cent.

Among 10,600 persons with smallpox reported during the five years between 1878 and 1882, non-vaccinated individuals were found to amount to 6,690, or 63 per cent. During the last epidemic in the years 1907-1908, 1,527 non-vaccinated persons among 5,215 smallpox patients were found in one prefecture, i. e., in Hiolgo.

Kitasato adds: "Law breakers will be found in any nation where a vaccination law is enacted. The middle and higher classes of Japanese people never allow their children to go unvaccinated, but the lower classes, who constitute the majority of the nation, often neglect their duty." Kitasato also refers to the remarkably low smallpox mortality among the million men engaged in the Japanese-Russian war.

He concludes as follows: "The antivaccinationists are like those who would deny the benefit of sunshine; it gives them every joy and happiness, and yet they are so familiar with it that they are not aware of its good. They would come to know the vast protective power of vaccination had they once experienced the terrible outbreaks of smallpox in their communities in which thousands on thousands fall victims, while the vaccinated ones go freely through the epidemic without the least danger of contagion."

As indicating the opinion of the Japanese government of the value of vaccination, we may take its attitude toward vaccination in Korea. The total number of persons vaccinated in Korea in 1908 was 544,630. Japan has established thirty official committees of vaccination among the thirteen provincial Korean governments, and has appointed 600 official vaccinators among the district magistracies and prefectures. In addition, forty-eight non-commissioned official physicians have been attached to important local police stations to aid in the work of vaccination. (See abstract in *Literary Digest*, June 25, 1910, p. 1253.) It is evident that this vaccination campaign is costing Japan enormous sums of money, but this progressive nation recognizes that the work is of great importance to its development and to the development of Korea. In view of the attitude of the Japanese government (which is certainly in possession of all the facts concerning vaccination within its own domain), the criticism of English and American antivaccinationists interpreting the results of vaccination from afar and crying "failure," will convince no one save themselves.

INCIDENT SHOWING EFFICACY OF VACCINATION IN SPANISH-AMERICAN WAR

The following facts were supplied by General Leonard Wood to Dr. S. Weir Mitchell, and through him to Dr. Samuel G. Dixon, Commissioner of Health of Pennsylvania, who published them in a bulletin of the Department of Health.

Major Robert S. Woodson, Major U. S. Army, in an official report, said: "Oct. 20, 1898, I was ordered by General Wood to proceed to Gibara, Cuba, on the northern coast of the Province of Santiago." . . .

"Smallpox had assumed epidemic proportions in March, 1898, and had steadily progressed until on our arrival there were on conservative estimate 4,000 cases, with thirty deaths a day in the district."

"For thirty years there had been almost continual warfare and political unrest, and consequently but very little vaccinating had been done."

"The effect of vaccination seemed to be instantly to check the epidemic as though it had been swept from the district."

"The crowning feature of all in proving the efficacy of vaccination was the fact that the entire regiment, Second U. S.

Volunteers (Hood), all protected by vaccination, encamped practically in the towns of Holguin and Gibara, mingling freely with the inhabitants, exhibited an absolute immunity against smallpox, as not *a single case occurred in this regiment* during the six months' service in the district."

General Wood adds: "A large number of American soldiers under a fair state of discipline were sent into a county infected with the most virulent type of smallpox, where the death-rate was heavy and all sanitary conditions were against them, and although living for several months in towns infected with most malignant type of smallpox to which they were constantly exposed, not a single case occurred in the regiment."

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ANIMAL EXPERIMENTATION AND TUBERCULOSIS

"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—Charles W. Eliot.

E. L. TRUDEAU, M.D.
SARANAC LAKE, N. Y.

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Issued by the Council on Defense of Medical Research
of the American Medical Association

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ANIMAL EXPERIMENTATION AND TUBERCULOSIS

**E. L. TRUDEAU, M.D.
SARANAC LAKE, N. Y.**



ANIMAL EXPERIMENTATION AND TUBERCULOSIS

E. L. TRUDEAU, M.D.
SARANAC LAKE, N. Y.

ETIOLOGY

Everything that we know to-day of the etiology of tuberculosis, everything that has a direct bearing on the prevention and control of the disease, we owe to animal experimentation. Before the infectious nature of the tubercle became established by animal experimentation no advance was made in the knowledge of tuberculosis in any direction except in that of pathologic anatomy. From Sylvius,¹ who in 1695 first described tubercles and drew attention to their relation to pulmonary phthisis, up to the time of Klencke² in 1843, and even of Villemin³ in 1865, who were the first to demonstrate by inoculation experiments on animals the infectious nature of the tubercle—that is, in a period of 170 years—no advance was made in the etiology of the disease, and this long period was wholly occupied by studies of the pathologic anatomy of tubercle, scrofula, caseation, pulmonary tuberculosis, and discussions of their relation to each other and their classification. Knowledge of the exciting causes of these pathologic processes remained theoretical; they were principally attributed to hereditary tendencies, perverted humors, and various types of inflammation.

Klencke,² in 1843, was the first to demonstrate the infectious nature of "tubercle" by inoculating rabbits in the vein of the neck with "tubercle cells" and producing general miliary tuberculosis in these animals. Klencke, however, hardly realized the importance of his own dis-

1. Sylvius: *Opera Med. Traj. ad Rhenum..* 1695.

2. Klencke: *Untersuchungen und Erfahrung im Gebiete der Anatomie, Physiologie, Mikrologie und wissenschaftlichen Medizin*, Leipzig, 1843, i, Abschnitt 11; *Mikropisch-pathologische Beobachtungen über die Natur des Kontagium*, Paragraph 24. See also ii, Abschnitt 1, Par. 16.

3. Villemin, J. A.: *Cause et nature de la tuberculose* (first memoir), 1865. *Etudes sur la tuberculose*, 1868.

covery, and little attention was paid to his work until, in 1865, Villemin,³ by extensive and carefully controlled inoculation experiments on rabbits, confirmed Klencke's views and demonstrated beyond doubt the infectiousness of tubercle by reinoculation from animal to animal. He also obtained evidence of specificity, as control inoculations with other morbid material, such as cancer, pus, bits of pneumonic lung, etc., remained negative. He was as successful with material derived from the *Perlsucht* disease of cattle as with human tubercle, and thus pointed out the identity of the tuberculous process in man and animals. From his experiments he reached the conclusion that the tubercle itself had nothing specific in its histology, and that the disease must be due to a germ. Scrofula he considered sometimes tuberculous and at others non-tuberculous, as he could not always produce the disease in his experimental animals with scrofulous products.

Animal experiments were first used as a means of diagnosis by Marcket,⁴ in 1867, who demonstrated the tuberculous nature of material from suspected cases of tuberculosis by producing with it generalized tuberculosis in guinea-pigs, and Edwin Klebs⁵ demonstrated by animal inoculations in 1868 that the sputum of tuberculous patients contained an infective element which was capable of producing the disease in guinea-pigs. Damsche,⁶ in 1882, used animal inoculations to make a diagnosis of urogenital tuberculosis.

While Klencke's and Villemin's results were accepted, the strife for many years continued over the interpretation of these results. Meanwhile, the positive proof as to the infectiousness of tuberculosis, obtained by subcutaneous inoculation in animals, was supplemented by evidence brought to light by inhalation and ingestion of tuberculous material. Schweninger,⁷ in 1866, at first failed to infect dogs by inhalations of phthisical sputum, but later—1886—he succeeded; and Lippl,⁸ in

4. Marcket, William: *The Inoculation of Animals as a Means of Diagnosis in Tuberculous Phthisis*, Med.-chir. Tr., London, 1867, p. 437.

5. Klebs, E.: *Ueber Entstehung der Tuberkulose und ihre Verbreitung im Körper*, Virchows Arch. f. path. Anat., 1868, xliv.

6. Damsch: *Die Impfbarkeit der Tuberkulose als diagnostisches Hülfsmittel bei Urogenitalerkrankungen*, Deutsch. Arch. f. klin. Med., 1882, xxxi, 78 ff.

7. Schweninger, E.: *Ueber künstlicher Erzeugung der Tuberkulose*, Gesammelte Arbeiten von Dr. E. Schweninger, Berlin, 1886, i, 242.

8. Lippl: Amtl. Ber. d. 50. Versamml. deutsch. Naturforsch. u. Aerzte, 1877, p. 268.

1877, produced pulmonary tubercles in rabbits by insufflation of fluid sputum from man through a tracheal fistula. Tappeiner,⁹ in a series of experiments which lasted from 1877 to 1888, demonstrated beyond doubt the infectiousness of phthisical sputum by inhalation experiments, his results being confirmed also by Bertheau¹⁰ in 1880. Tappeiner, in 1880, had failed to infect rabbits by exposing them to the breath of coughing consumptives, and concluded that the infection must be conveyed, if at all, by dried sputum arising as dust, and not by the breath of the patient. The danger of this mode of infection received practical confirmation when his servant, whom he had warned to protect himself from inhaling the dust of the room in which the animals were confined, developed pulmonary tuberculosis and died of it. Giboux,¹¹ in 1882, however, succeeded in infecting rabbits by making consumptives cough in the boxes in which these animals were confined, and thus demonstrated, long before Flügge's classical experiments, the dangers of sprayed particles of sputum from phthisical patients.

Feeding experiments also added irrefutable evidence of the infectious nature of tuberculous material, as well as bringing many facts to support the hitherto unsuspected identity of the *Perlsucht* disease of cattle and human tubercle, by proving that both produced tuberculous disease in animals when taken into the stomach. Chauveau,¹² in 1868, infected calves by feeding them bovine tuberculous masses, and Edwin Klebs,¹³ in the same year, infected guinea-pigs by feeding them with the sputum of consumptives, and in 1870 by the ingestion of bovine tuberculous material, which led him to the conclusion that the *Perlsucht* disease of cattle and human tuberculosis were caused by the same virus. Gerlach,¹⁴ in 1870, demonstrated the infectiousness of milk

9. Tappeiner: Amtl. Ber. d. 50. Versamml. deutsch. Naturforsch. u. Aerzte, 1877, p. 269. Wien. med. Presse, 1877, No. 43.

10. Bertheau, H.: Zur Lehre von der Inhalationstuberkulose, Deutsch. Arch. f. klin. Med., 1880, xxvi, 523.

11. Giboux: Inoculabilité de la tuberculose par la respiration des phthisiques, Compt. rend. 1882, xciv, 1391. Centralbl. f. d. med. Wissenschaft., 1882, p. 716.

12. Chauveau, A.: De la transmission des maladies virulentes par l'ingestion des principes virulents dans les voies digestives, Gaz. de Paris, xlvi, 1868.

13. Klebs, E.: Beiträge zur Geschichte der Tuberkulose. Virchows Arch. f. path. Anat., 1868, xliv, 278. Zur Geschichte der Tuberkulose, Virchows Arch. f. path. Anat., 1870, xlix, 291.

14. Gerlach, A. C.: Ueber die Impfbarkeit der Tuberkulose und der Perlsucht bei Tieren, sowie über die Uebertragbarkeit der letzteren durch Fütterung, Virchows Arch. f. path. Anat., 1870, li, 297.

from tuberculous cows by ingestion experiments on animals, and concluded that such milk was dangerous for human beings. Chauveau,¹⁵ in 1873, fed asses, horses, cattle, and 160 calves, with various kinds of tuberculous material for six weeks, and not a single animal escaped infection.

HISTOLOGY

Animal experimentation has also greatly advanced our knowledge of the histology of tubercle, and during the period from 1862 to 1882 the animal experimentation method was applied to its study, and many experiments were made to prove and disprove the specificity of tubercle from the histologic standpoint. In 1873 Virchow¹⁶ considered giant cells a criterion of tuberculous tissue, and as late as 1880 had reached the erroneous conclusion that *Perlsucht* of cattle and human tuberculosis were not identical, and that bovine lesions should be classed with lymphosarcoma. The findings of pathologic anatomy, however, were reversed by animal experimentation when Heidenhain,¹⁷ in 1872, and Weiss,¹⁸ Rustizky¹⁹ and Zielanko,²⁰ in 1875 to 1878, proved by experiment on animals that giant cells could be produced experimentally with powdered glass, muscle, bone, etc., and Cohnheim and Salomonsen,²¹ in 1877, from evidence based on eye inoculations in rabbits, added irrefutable evidence to the view that *Perlsucht* and human tuberculosis are inoculable, and are caused by the same virus; and established transmissibility to susceptible animals as the true and only reliable criterion of the tuberculous nature of any pathologic lesions. By this criterion the unity of scrofulous and tuberculous disease in man and animals, so long opposed by Virchow, was established.

Thus animal experimentation demonstrated beyond doubt the infectiousness of tuberculous matter in man

15. Chauveau, M.: Rec. de méd. vét., 1872, 1873. Cited by Johne, A.: Die Geschichte der Tuberkulose, Leipzig, 1883, p. 30.

16. Virchow, R.: Ueber die Perlsucht der Haustiere und deren Uebertragung durch die Nährung, Berl. klin. Wchnschr., 1880, Nos. 14 and 15. Die Uebertragbarkeit der Perlsucht durch die Nährung, Virchows Arch. f. path. Anat., 1880, lxxxii, 550.

17. Heidenhain: Ueber Verfettung fremder Körper, etc., Inaug. Diss., Breslau, 1872.

18. Weiss: Ueber der Bildung und Bedeutung der Riesenzellen, etc., Virchows Arch. f. path. Anat., lxviii, 67.

19. Rustizky, J. von: Untersuchungen über Knochenresorption und Riesenzellen, Virchows Arch. f. path. Anat., lix, 218.

20. Zielanko: Arch. f. mikr. Anat., cxI, No. 3, cited by Ziegler: Die Herkunft der Tuberkelemente, 1875.

21. Cohnheim and Salomonsen: Sitzungsber. d. schles. Gesellsch. f. vaterl. Kultur, July 13, 1877.

and cattle, the danger of tuberculous sputum and milk, and the identity of scrofulous disease and tuberculosis in man, as well as tuberculous disease in animals, by subcutaneous injection, by inhalation, and by ingestion experiments on animals, and established the value of animal inoculations in the diagnosis of suspected tuberculous disease (a method which gives evidence from which there is no appeal) before the birth of bacteriology and before the tubercle bacillus was discovered by Koch.

Koch's²² epoch-marking paper on the etiology of tuberculosis, announcing his discovery of the tubercle bacillus as the direct cause of all tuberculous and scrofulous diseases in man and animals, appeared in 1882. The unbroken chain of evidence forged by Koch in his logical demonstration of proof was obtained entirely by carefully controlled animal experiments, and gave the world a discovery of incalculable importance to the human race. Koch confirmed Cohnheim's views as to infectiveness being the best criterion of tuberculous disease, and by animal experiments established the value of microscopic search for the bacillus in diagnosis, and the identity of many lesions hitherto looked on as due to different diseases on account of the marked differences they presented both clinically and in the pathologic findings. He proved that all contained the same bacillus, which, when cultivated outside of the body, produced by inoculation in animals typical tuberculous lesions. Miliary tuberculosis, fibrous phthisis, caseous pneumonia, as well as scrofulous disease of glands, bones, and lupus of the skin, also *Perlsucht* in cattle, he showed to be due to the same cause—the tubercle bacillus.

PROPHYLAXIS, DIAGNOSIS AND THERAPY

In 1890 Koch²³ demonstrated by careful animal experiments the diagnostic value of tuberculin, pointed out its specific action on the course of the disease and on tuberculous lesions, and proposed the tuberculin test as a practical and efficient method of eradicating tuberculosis from infected herds, and tuberculin injections as a therapeutic measure in the treatment of the disease in

22. Koch, R.: Die Aetiologie die Tuberkulose, Berl. klin. Wchnschr., 1882, No. 15.

23. Koch, R.: Deutsch. med. Wchnschr., Nov. 13, 1890, No. 46a; Oct. 22, 1891, No. 43.

man. The discovery of tuberculin was entirely based on animal experimentation, and the value of this agent in the control of cattle tuberculosis, as an aid to early diagnosis of tuberculosis in man, and as a therapeutic agent in the more chronic types of the disease, can hardly be overestimated.

Animal experimentation has been of incalculable value in the diagnosis of obscure cases, and in teaching where the infectious material lurks and how to formulate effective measures for the prevention of the disease. By animal experiments the infectiousness of various secretions from the tuberculous was established. Edwin Klebs,²³ in 1868, proved the infectiousness of sputum; Gerlach,¹³ in 1870, the danger to man from the ingestion of the milk of tuberculous cows. Cornet's²⁴ exhaustive animal experiments demonstrated the danger of dried sputum, and indicated one of the principal modes of infection to be by inhalation of dried particles of expectorated material contained in dust from rooms inhabited by consumptives. Flugge,²⁵ by animal experiments, proved the danger of droplet infection in the immediate neighborhood of the consumptive by the spraying of small particles of saliva in sputum in violent coughing. Animal inoculations of the dust of infected rooms have also been used to test the efficiency of the measures to guard against room infection. This was done by Hance,²⁶ at the Adirondack Cottage Sanitarium in 1895. The entire system of hygienic care of the sputum and other discharges has been built up on the results of animal inoculations.

Not only have animal experiments been used in demonstrating where the infectious material lurks, but, since the discovery of the tubercle bacillus, the same method has taught us the various channels by which the bacillus gains access to his host, and all that we already know of the mechanism of infection and the defensive resources of the living organism. To Cornet's²⁴ exhaustive animal experiments we owe much of our knowledge as to the sources of infection and the channels whereby the tubercle bacillus gains access to the living organism. Through his work on the channels of infection, he found that in most cases the pathologic evidence should

24. Cornet, G.: *Tuberkulose*, Leipsic, 1890.

25. Flugge, G.: *Ztschr. f. Hyg. u. Infektionskr.*, 1899, xxx, No. 1.

26. Hance, I. H.: *Med. Rec.*, Dec. 28, 1895; Feb. 13, 1897.

furnish a clue to the site of invasion, but that tubercle bacilli are able to penetrate the macroscopically uninjured mucous membrane, and in rare cases even the skin, without leaving locally any evidence of their passage. This has been confirmed by many animal experiments in the recent exhaustive comparative studies of infection by inhalation and ingestion which have followed the world-wide discussion of the relative infectiousness of bovine and human tuberculosis.

Cornet²⁷ concluded that inhalation of infectious dust was the most frequent cause of infection, and that tuberculous infection progressed much more generally by the lymph stream than by the blood stream, and was rather a lymphogenous than a hematogenous infection.

Animal experimentation has taught us all we know of the complex, defensive mechanism by which the living organism resists the progress of bacterial infection and ultimately often heals the lesion and attains acquired immunity. Inspired by Pasteur's achievements in the field of acquired immunity, Daremberg,²⁸ Grancher, Martin,²⁹ Ledoux-Lebard,³⁰ Richet and Hericourt,³¹ and others of the French school attempted (with, however, but indifferent success) the production of artificial immunization against tuberculosis in animals.

The treatment of tuberculosis by tuberculin, as originated by Koch³² in 1890, was the first adaptation of the knowledge acquired by him in artificial immunization of animals to the treatment of tuberculosis in man. In America, Dixon,³³ in 1889, made experiments in this direction with attenuated bacilli; Trudeau,³⁴ in 1892, produced a marked degree of artificial immunity in rabbits with avian tubercule bacilli; and in 1893 de Schweinitz³⁵ obtained similar results in guinea-pigs by the use of bacilli of human origin attenuated by prolonged cultivation. In 1895 Theobald Smith,³⁶ by ani-

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- 27. Cornet: *Tuberculosis*, in Nothnagel's Practice, pp. 104-106.
 - 28. Daremberg, G.: *Compt. rend. hebd. Soc. de biol.*, Dec. 30, 1893, v.
 - 29. Grancher et Martin: *Congrès pour l'étude de la Tuberculose*, 1891, 1896.
 - 30. Ledoux-Lebard: *Arch. de. méd. expér.*, 1898, No. 10.
 - 31. Richet et Hericourt: *Etudes sur la tuberculose*, 1891, iii.
 - 32. Dixon, S. G.: *Med. News*, 1889, iv; *Med. and Surg. Reporter*, 1890, lxiii, 281.
 - 33. Trudeau, E. L.: *Med. News*, Sept. 3, 1892.
 - 34. De Schweinitz, E. A.: *New York Med. Jour.*, March 23, 1893.
 - 35. Smith, Theobald: *Tr. Assn. Am. Phys.*, 1896, p. 75; *Jour. Exper. Med.*, 1898, iii, 451.

inal experiments, demonstrated the differences of virulence between human and bovine bacilli, and thus opened the way for further studies in cattle immunization. Pearson and Gilliland,³⁶ by animal experiments, were among the first in America to attain a high degree of immunity in cattle by the use of the human type of bacillus. In Europe, during the past decade, von Behring,³⁷ Koch,³⁸ Calmette³⁹ and their associates, by extensive animal experiments, demonstrated the possibility of producing immunity by preventive inoculations in cattle of living human cultures, and advanced our knowledge of this complex problem of such overwhelming importance in man's struggle against tuberculosis to a point which may lead to its ultimate conquest.

Far-reaching in the saving of human life as the new knowledge of tuberculosis is, it is difficult to define accurately what it has already accomplished, because it has so recently been acquired and has, owing to the vastness and complexity of the problem, been as yet so imperfectly applied to both prevention and treatment, and because the results offered by the falling death-rate are in this disease influenced by so many factors other than those which bear directly on preventive measures aimed solely at the specific infecting agent, the tubercle bacillus.

The death-rate from pulmonary tuberculosis has fallen steadily in most countries during the last forty years, notably in England, where a decrease of 50 per cent. has taken place in that time.⁴⁰ In many countries it has fallen only slightly faster since the discovery of the tubercle bacillus and the more or less complete adoption of preventive measures, while in others it has fallen much more rapidly since 1882, as in New York City, where there has been during the past twenty years a reduction in the death-rate from pulmonary tuberculosis of nearly 40 per cent.,⁴¹ and notably in Prussia,⁴² where

36. Pearson and Gilliland: Philadelphia Med. Jour., Nov. 29, 1902, p. 842.

37. Von Behring, E.: Beitr. z. exper. Therap., 1902, No. 5.

38. Koch, R.: Schutz, Neufeld and Miessner: Ztschr. f. Hyg. u. Infektionskr., 1905, II.

39. Calmette and Guérin: Compt. rend. de l'Acad. d. Sc., 1906; Ann. de l'Ist. Pasteur, 1908, xxii, 689.

40. Osler's Modern Medicine, III, 145.

41. Handbook on Prevention of Tuberculosis, Charity Organization Society, 1903, p. 165.

42. Kayserling: Osler's Modern Medicine, III, 144.

the death-rate was 50 per cent. less in 1903 than in 1885. In some places, as in Boston, the death-rate during the twenty years preceding the discovery of the bacillus and the gradual adoption of preventive measures had shown no inclination to fall, while during the twenty years following this discovery it has fallen markedly and continuously. While it is true that the decrease in mortality began before any effective measures aimed directly at the infecting agent had been in force, the steady and continuous decrease in the death-rate makes it fair to assume that the brilliant results obtained have been due, in part at least, to the measures which aim directly at the limitation of the infection and the protection of the well from tuberculous dust.

In Boston⁴³ the death-rate, which in 1862 was 42 per 10,000 living, after slight variations, in 1882 was still about the same; but from 1882 to 1902 it fell from 42 to 21 per 10,000, so that during the past twenty-one years the diminution in the death-rate from tuberculous disease in Boston has been approximately 55 per cent., this decrease representing, in actual saving, 14,412 lives.

The demonstrable results in preventive measures aimed solely at the specific infecting agent would naturally be most noticed first in children, and the results in New York City, where such measures have been most strictly enforced, bring evidence in support of the influence of such measures on the death-rate of tuberculous meningitis and pulmonary tuberculosis in children. Dr. Biggs points out that "during the ten-year period ending 1902 there has been a decrease of more than 40 per cent. in the death-rate from pulmonary tuberculosis and tuberculous meningitis in children under 15 years of age in New York City, and that during a period of twenty years the decrease has considerably exceeded 50 per cent."⁴⁴

The results obtained, however, must depend greatly on the thoroughness and efficiency of the preventive measures adopted, and this perhaps has been best demonstrated thus far in the observations of Dr. R. W. Philip,⁴⁵ of Edinburgh. Dr. Philip, believing that partial measures were of little avail, and that effectiveness in preventive measures aimed at the control of the dis-

43. Massachusetts State Committee International Congress, 1908, p. 119.

44. Biggs: Arch. Pediat., May, 1904.

45. Philip, R. W.: Lecture before International Congress, 1908.

ease depended greatly on cooperation and coordination of all the agencies which tend to control the infection, gradually instituted a more and more comprehensive program in Edinburgh, in which all these agencies co-operated.

A study of the death-rate during the last twenty years in that city bears witness to the fact that the death-rate varies with the thoroughness with which the preventive program is carried out. The death-rate in Edinburgh was 19.5 per 10,000 in 1887. During the next ten years, when partial and uncorrelated measures were in force, it fell from 19.5 to 17, a percentage fall of 12.82; but during the following ten years, when a more comprehensive plan was adopted, it fell from 17 to 11 per 10,000, a percentage fall of 42.1 as compared with 12.82 during the preceding ten years, when a less efficient and comprehensive plan of prevention was in force.

Judging by what has been added to our knowledge of tuberculosis by animal experimentation in the past, it seems not unreasonable to entertain the hope that its ultimate control will be accomplished by knowledge acquired through the same means, and will probably depend not only on a more thorough and comprehensive application of the knowledge already won, on which all preventive measures are based, but also on the discovery of some specific method of immunization or treatment—a goal that can be attained only through continued and painstaking studies on animals.

NECESSITY OF ANIMAL EXPERIMENTATION FOR FURTHER ADVANCE

From the foregoing review of the history of tuberculosis, it would seem evident that everything that has a direct bearing on the prevention of tuberculosis, everything that has changed mankind's attitude toward it from one of apathy and hopelessness, when the infectious agent which produces tuberculosis was unknown and the disease was thought to be inherited and always fatal, to the growing hope of its ultimate conquest—a hope which has resulted in the great antituberculosis crusade spreading over the world and culminating in the late International Tuberculosis Congress in Washington—we owe to animal experimentation. If it were not for the knowledge which science has won by animal experimentation in the field of this disease in the last twenty-five years, we should still be plunged in the

apathy of ignorance and despair toward it which formerly prevailed, and tuberculosis would still be exacting its pitiless toll, unheeded and unhindered. Were it not for animal experimentation, the prospect of ultimately lifting this great burden of suffering and death from the human race would be as dark as it was before Klencke, in 1843, and Villemin, in 1865, succeeded in proving its infectious nature by experiments on animals with tuberculous material, and thus paved the way for Koch's discovery, in 1882, of the tubercle bacillus. The many researches which have flowed from the study of this germ have taught us already how to protect the healthy from infection and are daily teaching us how we may restore to health those already infected.

Thanks to animal experimentation, we know to-day that tuberculosis is not inherited; that it is communicable and, therefore, preventable; and that in its earlier stages it is curable.

Animal experimentation has taught us already much as to the different types of the tubercle bacillus, its virulence, the poisons it produces, and the manner in which it invades the living organism and destroys it. Slowly but steadily animal experimentation is teaching us the avenues of infection whereby the germ gains access to the organs of its living host; what are the defensive resources of the living organism; and the delicate mechanism whereby it combats the poison of the germ, tries to localize the bacilli, to limit their spread, and ultimately to destroy them. Animal experimentation is teaching us daily more of the complex and delicate processes which bring about acquired and artificial immunity, and through which the living organism wins the victory over the invading parasite. In the thorough knowledge and further study of these vital processes by animal experimentation lie the hope of applying to the protection of healthy human beings and the cure of disease, the knowledge won by science in studying Nature's methods of cure through long years of tireless and painstaking observations on animals.

During my lifetime all this knowledge, so practical in its bearing on the saving of countless human lives, has been won by animal experimentation. In my own personal experience, and as a result of my own observations, animal experimentation has led me to conclusions which have had a practical application in the treatment of my patients. In 1886 I was able to demonstrate on animals

the influence of a favorable environment on the disease. Inoculated rabbits placed under the most unfavorable conditions attainable, so far as light, air, food, exercise and surroundings were concerned, succumbed to the inoculation, while those turned out in the open air on an island and supplied with abundant food recovered, with only traces of the disease at the site of inoculation. These observations on animals increased my confidence in the influence of a favorable environment on the course of tuberculosis in man, and confirmed my faith in the value of the sanitarium and open-air method, of which I was then trying to make a practical application in the establishment of the Adirondack Cottage Sanitarium. The open-air and sanitarium treatment has already saved and prolonged, and will continue to save and prolong, countless human lives.

In 1893 animal experimentation gave me indubitable evidence that the production of artificial immunity against tuberculosis, which has always been looked on as impossible, was not as unattainable as was generally believed, my vaccinated rabbits and guinea-pigs showing increased resistance not present in the untreated animals; and this strengthened my faith in the value of continuing the study and use of vaccines in the treatment of tuberculosis. Although the progress made in this direction has been slow, the results obtained by many experimenters in many lands have been in accord as to the hopefulness of this line of research; the goal has almost been reached already in the vaccination of cattle through the experiments of Koch, von Behring, Calmette, McFaydean, Heymans, Pearson, and others; and the application of vaccines to the treatment of various infections in the human subject is extending and giving encouraging results.

The conquest of tuberculosis in man and animals, like the conquest of smallpox, of diphtheria, of rabies, anthrax, and many other infections through the production of some safe method of artificial immunity, seems, even to those hitherto skeptical, no longer visionary and unattainable. More knowledge of the infecting agent, its poisons, its methods of attack, the various defensive resources of the organism and methods that will call them into action, can be obtained only by animal experimentation.

Inoculation experimentations entail no greater suffering to the animal than the prick of a hypodermic needle,

and then a painless death if it be killed, or death from tuberculosis if it be allowed to live. Those who cry out against animal experimentation trust us with the lives of their families when sick, but fear to trust us with rabbits and guinea-pigs. Surely the motives of physicians who are trying to learn how to prevent and cure disease, when their livelihood depends on the practice of medicine, can hardly be called into question. Those who in their blind ignorance or through false sentiment are trying by legislative interference to stop or to restrict animal experimentation do not, as we doctors do, have to witness daily the ravages of this terrible disease and live in the midst of the suffering and sorrow which follow in its wake; they seem to be content that all this should continue indefinitely so long as they are not brought into contact with it.

The new knowledge of tuberculosis, of such overwhelming importance to the human race, a knowledge which already gives assurance that generations to come will not die of this disease to the extent that former generations have died, has been won in recent years by animal experimentation. For all this is the death of any number of guinea-pigs and rabbits too high a price to pay? Are we to stop on the threshold of this newly acquired knowledge, and are the fruits of ultimate victory to be denied to humanity? These would seem questions that could safely be left to the common sense of unprejudiced men.



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The Role of Animal Experimentation in the Diagnosis of Disease

"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—*Charles W. Eliot.*

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DEFENSE OF RESEARCH PAMPHLET III

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FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET
1913

which is somewhat conspicuous by a relative failure to attack the poor, the overworked, the underfed, and the savage, but chooses a notable proportion of its victims among the well-to-do, the well-nourished, the well-protected against infectious diseases, and the indolent. Cancer is a growing penalty on a one-sided civilization. It has as yet no place in sanitary science. The most conservative estimate must, therefore, admit that the situation in regard to cancer is ominous. This disease is the greatest of all physical evils in the higher animal kingdom and its unhindered ravages constitute a stigma on human intelligence which is not the less genuine because cancer is the most obscure and comprehensive problem of biology.

Thoughtful persons may well ask what science has done and what it is proposing to do for cancer.

In the first place, science—and exclusively medical science—has written the natural history of cancer. How it was accomplished has been told by Wolff¹¹ in a volume of 750 pages in which the labyrinth of detail, depicting the varying conflict of truth and error, does not obscure the magnitude of the task, the volume of labor expended, or the fascination of the narrative, which covers 2,000 years of human history. In this story, one is impressed by the fact that cancer research has been strictly limited by the progress of collateral sciences, and that the real progress of our knowledge has been contributed by relatively few men whose work was wholly beyond the reach of the public ken and whose results were depreciated or ignored by a considerable portion of the medical profession of their day.

The natural history of cancer has been very fully written, and to the surgeon belongs the credit of making practical use of this knowledge. The wisdom of an early recognition and complete removal of cancer by the knife is a lesson that has been thoroughly learned. Yet cancer is on the increase, and it must be seriously doubted if the earlier recognition of the disease and more effective removal will ever succeed in greatly reducing the mortality from its present figures. From the operating surgeon the cancer patient can hope only for an earlier resort and more frequent submission to the knife, and it is doubtful if this prospect has been any more abhorrent to the patient than to the surgeon.

11. Wolff: *Die Lehre von der Krebskrankheit*, Jena, 1907.
Wood & Co., 1908.

Cancer research also up to 1900 has offered little encouragement to the victim of the disease. The systematic study of the cancer process, having vainly exhausted its energy in the parasitic theory, had fallen into a state of hopeless inertia. Medical science had branded this field as fruitless. Laboratory workers who were looking for results turned with dismay from the uninviting prospect. But in 1902 cancer research sprang into intense activity. New ideas riveted the attention of laboratory workers on this subject. Local, national and international societies were formed for the study of cancer along new lines. Broadly organized institutions supported by enlightened governments, universities, and men of means, were established in England and Germany for the systematic pursuit of the new themes. Medical literature abounded with contributions in the new field, and two new journals were shortly established, devoted exclusively to this work. The change has been almost instantaneous and constitutes nothing short of a revolution.

What influence has been capable of bringing about such a change? It was the introduction of animal experimentation into the study of cancer.

The idea of transplanting cancer from one animal to another was not new. Peyrilhe¹² tried it about 1780, when France was not ready for such work. Surgeons had long recognized that they never contracted cancer during operations in such cases, and Alibert¹³ found that he could not inoculate himself or his assistants with the disease. Scores of observers had wholly failed in many attempts to transfer the disease from one animal to another, so that it was generally accepted that cancer was not inoculable. Yet in 1889 Hanau's¹⁴ report of the successful transfer of an epithelioma from one rat to another excited much passing interest in Germany. In the same year, in France, Moreau¹⁵ had very definite success in eight out of ten mice inoculated with a carcinoma of a mouse, and by 1894 he had carried this tumor through seventeen generations, making the first experimental observations on the influence of gestation and heredity on tumor growth. It was not until 1901 and

12. Peyrilhe, cited by Wolff: *Die Lehre von der Krebskrankheit*, p. 65.

13. Alibert, cited by Pianese: *Beitr. z. path. Anat. u. z. allg. Path.* (Ziegler's), 1896, Suppl. 1.

14. Hanau: *Arch. f. klin. Chir.*, 1889, xxxix, 678.

15. Moreau: *Arch. de. méd. expér. et d'anat. path.*, 1894, vi, 677.

1902, when Loeb¹⁶ in America and Jensen¹⁷ in Denmark reported their systematic studies of transplanted cancers in rats and mice, that the great importance of this work became recognized. It was now seen that it was possible by animal experimentation to study the growth of tumors under the exact conditions of a laboratory experiment. The same methods which had proved successful with smallpox, cholera, diphtheria and tuberculosis were now made available for cancer research.

Accordingly the experimental study of cancer has been taken up energetically in England, Germany, France, Austria, Japan and America, with the result that in five years new facts of first importance have been demonstrated and the entirely new field of cancer immunity has been thrown open. It is too early to place a final estimate on the true value of many of these facts, but present indications point out some of the results as most significant and as revealing the revolutionary influence of the experimental study of cancer.

1. In 1862 Virchow¹⁸ stated that no human being could define, even under torture, exactly what a tumor was. To-day we know, at least for cancer, that the final criterion is the capacity of a tumor cell to maintain an independent existence when transplanted into an animal of the same species, and this test has been successfully employed in several doubtful cases.

2. A sensational feature of the recent studies is the demonstration that cancer cells may apparently grow forever, if suitable environment be provided. The Jensen strain of mouse tumor has been transplanted through several hundred generations over a period of seven years and still shows undiminished vitality. There is good reason to believe that a certain sarcoma of dogs readily transmitted by coitus has acquired its very great infectivity by repeated natural transfers in this manner and thus constitutes a wholly new form of parasitism.

3. It has been shown that the conditions under which transplanted tumor cells will grow are extremely narrow, vastly more so than those governing the growth of bacteria. Haaland's cancer grew well in Berlin mice fed on milk, but when an attempt was made to transplant this tumor into Copenhagen mice of exactly the

16. Loeb: Jour. Med. Research, 1901, vi, 28.

17. Jensen: Centralbl. f. Bacteriol. u. Parasitenk., 1903, xxxiv, 122.

18. Virchow: Die krankhaften Geschwülste, 1863, i, 3.

same species, but fed on carbohydrates, great difficulty was encountered. The slight difference in the diet sufficed to render the soil refractory. Such a result encourages the hope that it may prove possible to influence the growth of established tumors by practical therapeutic measures, although previously there seemed to be no ground for such a hope.

4. The question of the spontaneous cure of malignant tumors had long been debated and remained uncertain until such spontaneous regression had been repeatedly observed in transplanted tumors of mice, rats and dogs. This observation was so contrary to the well-established belief that malignant tumors never spontaneously regress that its occurrence in lower animals was at first vigorously denied, and only repeated demonstration compelled its final acceptance.

5. Most significant is the discovery that there is such a condition as immunity to cancer. Most animals that have recovered from tumors either spontaneously or after incomplete operation are thereafter immune to cancer. Not only may this immunity be established after spontaneous cure, but it has been artificially induced by inoculation with extracts of normal mouse organs and embryos. It is hardly possible to overestimate the importance of this discovery, since it at once takes cancer from a realm of baffling obscurity and places it in much the same position as the infectious diseases. The nature of this immunity is very complex. New methods must be devised for its study, but the possibility of perfecting these methods exists and solely as the result of animal experimentation.

6. After repeated transplantation cancers have been found to increase in rapidity of growth and in the capacity to survive transplantation; i. e., they acquire increased virulence. This wholly unexpected result, which might appear to be of no practical significance, has been used to produce artificial immunization, for by vaccinating an animal with a feeble strain of tumor from which it recovers, the animal becomes immune to the most malignant cancers. The principle of a preventive treatment of cancer has thus been disclosed.

7. Medical science has spent many years and much labor in the vain effort to discover a parasite of cancer. Even recently it has been feared that cancer patients were a menace to their neighbors, and that the houses of cancer victims should be burned. But the experimental

study of tumors has greatly strengthened the view that cancer is not a contagious disease, that its exciting cause cannot be a readily transmissible parasite, and that the long-looked-for cancer parasite is the cancer cell. The field of research has, therefore, been narrowly defined, and it is not likely that the enthusiastic search for a specific cancer parasite will soon again assume the dominant position it once occupied.

8. The relation of heredity to malignant tumors has formed a vital chapter in cancer research, but based on the uncertain observations of family histories the most divergent views on this subject are extant, and exact knowledge about the nature of any hereditary influence in tumor growth is lacking. Are the offspring of two cancerous parents especially liable to develop the disease, and, if so, to what extent, and what course will the disease take? No one knows. Yet the early observations of Moreau bore directly on this subject, and in the short-lived mouse it is possible to devise experiments of reasonable time-span which will definitely settle some of these questions. In several laboratories such experiments are already well advanced, with preliminary results of great interest and importance.

9. The rational cure of established cancer in man remains a problem for the future. Mice have been cured by serum therapy, and in nine consecutive cases a malignant sarcoma in dogs has been cured by bleeding the animal and transfusing it with the blood of dogs immunized to this tumor. But the cure of advanced cancer in a human being presents many peculiar difficulties. It may be unsafe to make any predictions, but it is certainly legitimate to claim that the therapeutic principles established in lower animals will prove applicable in some form to man for cancer as for diphtheria. Hence we may endorse the statement of Ehrlich,¹⁹ that the beginning of the end of the cancer problem is in sight. By the systematic pursuit of the principles of cancer growth and immunity already discovered by means of animal experimentation we may confidently hope to prevent some cancers, to check others, and greatly to reduce the incidence and mortality of this disease.

These are some of the practical results of the new era of experimental cancer research. From the stand-

19. Ehrlich: Arb. a. d. k. Inst. f. exper. Therap. zu Frankfurt a. M., Jena, 1906, p. 78.

point of rational therapeutics the results of five years' work by the experimental method overshadow those of the thousand years preceding. Medical history offers no similar demonstration of the wisdom of absolute freedom for science in the use of animal experimentation. Thousands on thousands of fruitless efforts extending over at least a century were made to transplant tumors before a single definite success was secured. Yet it is said that needless repetition of experiments ought to be checked. Moreover, these results have not been reached without bitter controversy. Every step of the way has been energetically contested. Many loudly proclaimed that the experimental tumors of lower animals were not true cancers. Yet it is now known that every essential property of human cancer is exhibited by the cancers of mice, rats, and dogs. The immediate requirements of the practicing surgeon, and some theoretical burdens of the physiologist and biologist and of other scientists interested in cancer, have perhaps not been affected in a startling manner, so that in some quarters appreciation of the true value of this work may be slow. In the rear of every army of progress there is a scattered following of disaffected non-combatants, and modern cancer research has, therefore, been pronounced wholly fruitless by some uninformed persons.

To all critics, whether helpful or destructive, the answer must be that there is no prophet directing cancer research. No doubt posterity will be able to look back to the beginning of the twentieth century and point out that this or that piece of work was not in the direct line of progress. But here and now the most mature, although uninspired, human judgment says that genuine progress has been made into the dark domain of cancer pathology by means of the experimental method; that this knowledge could be acquired in no other way; and that these principles must be mastered before the cure of human cancer can be devised or attempted. Some critics seem to assume that the concentration of interest on the experimental studies has distracted attention from other equally important branches of the subject. But not the least valuable result of the experimental work has been the renewed impetus given, and the new view provided for the investigation of such topics as the inception of tumor growth, the laws of nutrition of tumor cells, and the influence of neoplasms on the body.

In view of the great significance of cancer for the animal kingdom, especially for man, and of the sudden transformation of the gloomy aspects of the problem wrought by the introduction of the experimental method into this field, what is the duty of the layman toward animal experimentation and cancer? Who may dare to lay obstacles in the way of this progress, or to obstruct the ray of hope that begins to shine for the victim of cancer? In America the workers in this and allied subjects look forward with confidence to the moral support of every intelligent person, and even anticipate that men of large minds and large means will come forward and adorn the land with one thoroughly organized and fully equipped institution for cancer research.

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THE ETHICS OF ANIMAL EXPERIMENTATION

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DEFENSE OF RESEARCH PAMPHLET V

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

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FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
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THE ETHICS OF ANIMAL EXPERIMENTATION

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[Editorial Note.—James Rowland Angell, born 1869, Burlington, Vt. A.B., University of Michigan, 1890; A.M., Harvard, 1892. Instructor in Psychology, University of Minnesota, 1893. Assistant Professor of Psychology, University of Chicago, 1894; Associate Professor, 1901; Professor and Head of Department, 1904. Director of Psychological Laboratory, Dean of Faculties of Arts, Literature and Science, Member of Council of American Psychological Association, 1903-06; President, 1906. Author of "Psychology," Henry Holt, New York, 4th ed., 1908; numerous monographs and papers in technical journals].

Is man morally justified in causing animals pain, and, if so, under what conditions? This is the moral issue raised by the practice of animal experimentation. The attitude of the average person on this question is no doubt more likely to be determined by temperamental bias and accidental prejudice than by any clear vision of fundamental principles. Nevertheless, it seems worth while in this day of increasingly bitter controversy over the experimental use of animals to inquire somewhat closely into the ethics of the case.

Historically, we find two fundamentally divergent views entertained on the general subject. Most widely prevalent—and sanctioned at one time or another by religious practices among all peoples—is the view that man is the overlord of the animals and may use them for his pleasure and profit, even to the point of robbing them of life. This view undergoes much softening and is hedged about with humanitarian restrictions among the more highly civilized races. Over against this is the belief that man has no right to take animal life or cause animal suffering. Buddhism, with its belief in the transmigration of souls, is the great religious embodiment of this view, although it has perhaps seldom gained a

strictly consistent execution in practice. In estimating the import of this radical discrepancy in moral principles, one naturally looks to the origin of moral belief as possibly affording illumination.

Moral principles have generally derived their power over human action from one or more of three distinct sources: (1) They have been accepted as embodying divine law implanted in the consciousness of each individual, or revealed through the inspiration of holy men. This is the intuitive view of morals. (2) They have rested on custom, law, or social and political usage. This is the traditional view. (3) They have been justified by the happiness and social welfare which it is believed follow on obedience to them. This is the scientific view.

Under no one of these conceptions of the origin of morality do we find immediate and unambiguous guidance in the problem of animal experimentation. Religious teaching is equivocal. Certainly most of it sanctions the taking of animal life, and the consciences of primitive people at least seem to cause them no distress, even when they torture dumb creatures. Custom has varied among different races, but, in the main, has undoubtedly favored the treatment of animals in accordance with the unbridled wishes of man. Even among civilized peoples, gelding, dehorning and other mutilations of animals are countenanced under conditions which unquestionably occasion much suffering. At the present time controversy is carried on almost wholly under the ruling conceptions of the third division—i. e., the issue is argued as one of fact concerning the consequences of animal experimentation. In any event, this is the only point at which argument may hope to convince the open-minded, one way or the other. Obviously, the argument from custom proves nothing and convinces nobody. The man who believes in the transmigration of souls between human and animal forms cannot be dealt with in the limits of this paper, but in the Anglo-Saxon world, at least, he is to all intents and purposes non-existent. Certainly the great mass of modern critics of experiments on animals do not rest their case on any such foundation. They assert that needless pain is an unmitigated evil, and that its gratuitous and intentional causation is a sin and a crime. They allege that animal experimentation is (1) not justified by any results it has yet attained and (2) that it is demoralizing and

brutalizing in its influence, both on those who conduct it and those who observe it.

Certain more conservative critics urge that, although its occasional employment has resulted in justifying benefits both to man and the animals, it is done far too extensively, is done when the results cannot possibly justify it, and done carelessly and with indecent disregard of all the humanities. Clearly, this is an indictment drawn on alleged facts, and no verdict can be rendered without an examination of the facts.

If it be granted, however, that the experimental procedure is ever justified by its results, the basal ethical issue is closed. It only remains to make sure that in a given case the warrant is certainly adequate, that the minimum of pain is caused the creatures used, and that the indirect effects on the public and on students are not such as to augment the spirit of cruelty or insensitiveness to suffering.

Fortunately, or otherwise, we have no calculus by which we can estimate the amount of pain caused an animal by a given experimental operation, or the amount of suffering saved to other creatures as a possible result of its sacrifice. But with the literally inestimable benefits which are daily being reaped in the prevention of smallpox and in the amelioration or prevention of diphtheria—to mention only these two cases, out of a rapidly lengthening list—it is difficult to understand how any one can honestly frame a sweeping indictment of operations on animals to which these victories and others like them are unquestionably due.

As a matter of fact, the case is somewhat complicated in the public mind by the appearance among the extremer critics of not a few gentlemen who sign themselves M.D., and who claim a professional knowledge of the details of the case. To be sure, the overwhelming majority of medical men, including all the great leaders of the profession and all the great medical organizations, are staunch defenders of animal experimentation.

It would be ridiculous to pretend that all operations on animals have such striking justification, either in purpose or in result, as those which led to the discovery and perfection of vaccine or antitoxin. Many of them frankly fail to result in immediate scientific progress, and many are done for purposes of instruction, the beneficent results of which are always uncertain and frequently long deferred. But, as has been said above,

the fundamental ethical issue is closed, once it be granted that there are *any* conditions under which animal experimentation is justified. The problem which remains is simply that of determining the circumstances and conditions which warrant particular forms of the method.

Just at this juncture arises a peril which medical men justly fear. Who shall determine what precautions are to be thrown around animal experimentation, who shall be allowed to undertake it, and what circumstances shall be held to justify it? At this point the opportunity opens for unintelligent and officious interference such as might well jeopardize medical advance for a generation to come. It is sincerely to be hoped that sentimental considerations, however honestly intended, will not be allowed to rob those most able to judge wisely and fairly of these matters, of the power of control, which should be in their hands.

When we inquire what, in a practical way, honest and humane people would consider sufficient justification for experimental operations on animals we meet all the vagaries of personal idiosyncrasy. For one, only the saving of human or animal life in large numbers would justify the procedure. For another, adequate reason would be found in a mere lessening of pain, even though the question of death were not involved. For still another, any advance in scientific knowledge which might in the future conceivably conduce to human or animal welfare would afford sufficient justification. Evidently we are here plunged in the waters of casuistry, where it is hopeless to follow. Biologic scientists generally hold the third view mentioned. Probably the rank and file of the lay public would espouse the second view; while a few sensitive souls, especially those of vegetarian proclivities, hold the first view. Finally, in a still smaller group, are those extremists who will hear of nothing but the absolute prevention of animal experimentation.

Those who approve animal experimentation at all, except perhaps men of science, are no doubt moved by the same general motives which lead us to approve whatever is customary and familiar. We harness the horse and force him to work for us, whether he likes it or not. We rob the cow of her calf that we may ourselves enjoy her milk. In like manner we rob the hen of her eggs and think no worse of ourselves for the larceny; and, finally, we wind up our tale of coercion by a ruthless

slaughter, for food or sport, of both bird and beast, wild and domesticated alike. With such customs in vogue about us, it is not strange that most persons should lend a willing ear to the defenders of properly controlled experiments on animals. The only wonder is that so many persons have been willing, on imperfect and misleading evidence, to countenance and even endorse the advocacy of repressive measures of the most drastic sort —measures entirely unwarranted when judged by the prevalent practices in the treatment of animals in every other human relation. Not that one would wish to justify a bad practice because other worse ones were in operation. But when one takes a sensational account of the torturing of animals in some surgical laboratory, and judges the case without any regard to an examination of the precautions taken to secure anesthesia for the animal, and without any regard to the prevalent ethical sense concerning the extent to which animals may be sacrificed for human welfare, one obtains a morally distorted and unbalanced point of view, from which no sane judgment can be expected to emanate.

In the main, modern opinion cannot be made to take seriously the view that all animal life should be sacred. As soon as the mosquito was convicted of responsibility for yellow fever and malaria his days among civilized men were numbered. He was always a nuisance. Now he is a homicidal criminal. It may take some time to exterminate him, but he can no longer find any intelligent human defender. Let us hope that the fly will similarly be put under an everlasting ban. Assuredly his responsibility in the matter of typhoid and other filth diseases has been abundantly demonstrated. Poisonous serpents and vermin of all sort have long ceased to enjoy any considerable immunity from slaughter. In a practical way, insects are apt to be thought of as being outside the pale of ordinary humanitarian consideration; but if one is going to inquire seriously into the ethics of our human relations to animal forms, one must recognize that the justification for protecting insect life is neither greater nor less than that for protecting the higher animals, provided any of them menace human welfare. And if interference with their lives be permitted on the ground of human welfare, the avenues are at once open, so far as morality is concerned, to the various forms of operations on animals.

The trend of modern opinion among civilized people is unquestionably toward a more drastic application of the principle of the right of society to protect itself. The criminal is punished not primarily in retribution, but in order that society may not suffer further his evil doings. Temperance legislation, whether wise or not, is designed not only to help the drunkard, but particularly to remove temptation from the path of the innocent. Quarantine is possibly the best illustration of protective social interference with individual freedom. Often the isolation of a patient suffering with contagious disease may operate to endanger his life. But the danger to the community arising from failure to isolate him is commonly adjudged a greater evil. And so at the risk of harm to the patient the community protects itself. How much more, then, for people who assent to the logic of this principle and to its moral justification, should the use of animals seem warranted, when such use can be made widely contributory to the decrease of suffering, both human and animal? Of course, if one entertains the "Christian Scientist" view of the illusive character of pain and disease, all these conclusions fall to the ground. But, on the same principle, there would be no justification for doing away with the mad dog and the venomous serpent. And, in any case, the "Christian Scientist" is not likely to be influenced by any ordinary considerations on this matter, either one way or the other.

Not only is the right of society to protect itself against crime and disease gaining daily a wider recognition, it is also true that the public is coming to a juster appreciation of the relation of science to social welfare. Science has too long masqueraded in the popular mind as a realm of impractical theory, touching the life of the common man only in the most remote way. The contemporary world appreciates increasingly the fallacious character of this view. In industry, in commerce, in medicine, and even in government itself, the scientific knowledge of yesterday is the basis of the practical device of to-day. Science is simply the intellectual aspect of social progress, and, when this conception is still more familiar than it is at present, we shall hear less of the *merely* scientific interest in animal experimentation, as though there were any genuinely scientific interest which could escape contribution to social advance. Certainly, biologic science, quite as well

as pure medicine, ought to be given freedom to pursue its researches in the general interests of mankind, with such methods as may commend themselves to investigators. To obstruct biologic science by a general prohibition of experiments on animals, or to obstruct any other science by proscribing approved methods, is to sin against the light and to turn back the hands of progress. No thoughtful person is likely seriously to commend such a course.

The question as to the moral effect of the practice of animal experimentation on persons who engage in it or observe it is difficult to dispose of effectively. Undoubtedly most persons feel a squeamishness about their first operation on an animal, which later on they lose, and the critic of the practice is likely to interpret this fact as meaning that the practitioner has become callous and indifferent to suffering. I see no reason to deny that this result may occasionally occur. But in every reputable laboratory the usages are as humane as the circumstances will permit, anesthesia is the universal practice, and it is perfectly certain that the total amount of suffering which the animals undergo is negligible in comparison with that which confronts most of them in a state of nature. Moreover, a loss of the original squeamishness is by no means synonymous with a loss of practical tender-heartedness. It may act simply to insure a steadier and prompter hand, with a corresponding decrease in the length of time occupied by the operation and an increased chance of a favorable outcome. It should be remembered, too, that the selfish interests of the operator almost inevitably and invariably make it to his advantage that the animal should suffer as little as possible, in order that its vigor and vitality may be at the maximum. It should also be added that, just as many surgeons are most tender-hearted, despite their apparent indifference to the suffering of their patients, so many men who do a large amount of operating on animals are keenly alive to the welfare of their animals. But even if all experimenters were hardened by their work into a disregard of animal pain, society might still pronounce the value of their results to outweigh this drawback. In the larger view which looks to the ultimate welfare of society as a whole, such men are among its most valuable humanitarian members, whatever their personal attitude toward the animals with which they work.

In conclusion, then, it may be said that we find no obstacle to the practice of animal experimentation in any intuitive moral convictions, nor in the traditional morality of our own race. When we try to estimate its justification in terms of its results, we find that it has precisely the same kind of warrant as that which attaches to all our great social enterprises, in each of which we are ready to sacrifice a lesser good for a greater good, and are willing to encounter a moderate evil in order to escape a greater evil. For the sentimentalist, to whom all thought of gratuitous suffering is abhorrent, probably no argument can ever avail to justify certain forms of experimental procedure. On the other hand, to the man familiar with the revolutionary advances in science and medicine which have originated in the experimental use of animals its condemnation seems the last word of a pernicious insanity. To the great public, representing the intermediary between these extremes, it is to be hoped that a calm and discriminating judgment may be vouchsafed, and one which takes into account all angles of the case. In the long run we have confidence in the integrity of our public judgments on moral issues. In a case so serious as this, we need the highest degree of deliberation, sobriety, and intelligence.

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ANIMAL EXPERIMENTATION

THE PROTECTION IT AFFORDS TO ANIMALS THEM-
SELVES AND ITS VALUE TO THE LIVE-STOCK
INDUSTRY OF THE COUNTRY

VERANUS A. MOORE, M.D.

Director New York State Veterinary College at Cornell University
ITHACA, N. Y.

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Issued by the Council on Defense of Medical Research
of the American Medical Association

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VERANUS A. MOORE, M.D.

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ITHACA, N. Y.**

In subjecting to a careful analysis the results that have accrued from animal experimentation it is not easy to separate many of those which have benefited brute creation from those which have tended more or less directly to alleviate some form of human suffering. The animal experiments which led to the discovery of the facts that form the basis of our present knowledge of the action of the heart, the circulation of the blood, the mechanism of respiration, the functions of the various organs, the action of drugs, the causes of epizootics and the effects of different foods, are generally omitted in pointing out the extent and value of our knowledge of these vital subjects. As the life conditions of lower animals have been greatly benefited by the acquisition of knowledge derived from such experiments, it is not unnatural that those interested in the well-being of domesticated animals should not only wish to continue but also to add to these benefits by the use of methods already demonstrated to be efficient. On the other hand, the supporters of the propaganda against animal experimentation wish the work to be discontinued. In their arguments they fail to take into account the source of the very knowledge of physiology and pathology which they are pleased to possess, denounce the methods by which it was acquired and imply that we already possess sufficient information on subjects of this kind.

In the endeavor to ascertain the rightfulness of animal experimentation or to justify its continuance, we are confronted at the outset with certain basic questions,

the answers to which must determine whether or not the routine, the investigations and the research which involve animal experimentation shall or shall not be stopped. These questions are: Shall the process of evolution of the knowledge of physiology and the diseases of animals and their prevention be arrested? Shall efficient methods of treatment be discarded? Shall the domesticated animals, dependent, as they are, on man for their protection, be subjected for future generations to the merciless cruelty of bacterial and protozoan diseases without the application of known methods to prevent them? Shall the animal industry of the country suffer continuously great losses from disease and death of animals because the methods of preventing them may cost the lives of a few individuals? Shall our export trade in animal products, which is carried on only because of the slaughter of millions of cattle, hogs and sheep, be interrupted, with all the attending consequences of this interruption in order to save the lives of a few experimental animals? In the interest of commerce, humanity and the animals themselves, the answer to each and all of these questions seems to be one and the same—no, emphatically no.

The spirit which dominates the work involving animal experimentation is the desire to add to our common knowledge new and important facts that will make possible the formulation of more efficient methods for preventing suffering and loss by death in the dumb creation. All further knowledge or better understanding of the subtle forces of Nature that produce disease and death in animals must be attained through the use of animals. The methods now in vogue for the control of epizootic diseases are based on the results obtained from animal experimentation. The diagnosis of an epizootic sometimes requires the use of animals, and many of the therapeutic agents as well as preventive vaccines demand the continued employment of living animals. No one uses sentient creatures experimentally from choice, but unfortunately there is no alternative. We must either use a few living animals as reagents and manufacturers of vital products, or subject our flocks and herds to the ravages of uncontrolled pestilences.

In the United States there are animals, exclusive of poultry, cats and dogs,¹ valued at \$4,331,230,000. The

1. Year-Book of the U. S. Dept. Agric., 1907.

United States¹ has an annual export trade in animals and animal products of \$254,798,329. The acquiring of this great wealth in animals and the commercial interests involved have been possible because of the somewhat successful methods that have been formulated and applied for preventing and controlling epizootic diseases. Without their control this country could not enjoy the present benefits of its export trade. As soon as an epizootic, like contagious pleuropneumonia or foot-and-mouth disease, appears, the foreign ports are closed to the importation of animals from the infected districts. The prevention of the severe losses formerly sustained in the northern part of the United States from Texas fever has been made possible by the acquisition of knowledge pertaining to its specific method of dissemination. These illustrations are sufficient, although others could be cited, to show the importance of maintaining as complete a control as possible of epizootic diseases. From the humane side of the question, a further reason for the subjugation of these diseases is found in the alleviation of the suffering to the animals themselves from the inroads of such diseases. Again, the loss occasioned by the epizootic diseases to the individual animal owners is not entirely determined by the value of the animals that die. This is measured in part by the attending human suffering from want and privation, brought about by the loss of animals that were the only source of revenue for the purchase of necessary supplies.

In times of prosperity it is not customary for even the more thoughtful to consider seriously the sequence of events which make the existing success in the traffic of animals and their products possible. The number of the infectious diseases to which our domesticated animals are susceptible, and the suffering and loss which they formerly occasioned, are generally either unrecognized or forgotten. A mere glance at their history will show that the infectious and epizootic diseases baffled all attempts at prevention until a knowledge of their specific nature was determined as a result of animal experimentation. These investigations showed that the epizootic diseases are due to infection with some micro-organism. In certain instances the specific organism has not as yet been discovered, but its means of transmission has been determined, while in others the specific

cause itself has been found. With this knowledge these animal plagues can be, and are, largely controlled. It is from the knowledge derived from animal experimentation alone that it has been possible to bring the great scourges of animals, like rinderpest, contagious pleuro-pneumonia, anthrax, Texas fever, rabies, foot-and-mouth disease, and many others, under the present state of subjugation. This has not only prevented untold suffering to millions of animals, but it has also saved them for their owners.

The fact should not be lost sight of that the diseases mentioned, as well as many others, are liable to be, and often are, reintroduced after they are successfully eradicated. This is illustrated by the destructive malady known as foot-and-mouth disease, which has been introduced and eradicated from this country at least three times.² This fact calls for constant vigilance and often the employment of preventive vaccines as well as other precautionary measures. The true conditions relative to the relation existing between our live-stock industry and the control of disease may be better understood by reviewing somewhat briefly the history of a few of the more important epizootic diseases.

ANTHRAX

Anthrax has been known since very early times. It was primarily a scourge of cattle and sheep, but often of other animals and of man. It caused annually the death of thousands of animals until its cause was discovered, its method of dissemination determined and a preventive vaccine brought out by Pasteur. The successful vaccination against anthrax by the use of attenuated virus which was demonstrated to the satisfaction of the scientific world by Pasteur³ robbed anthrax of much of its terror for the cattle owners and enabled farmers to keep live stock in many localities where otherwise it would have been impossible. This was also true in America. The work of Chester⁴ in Delaware, in the production and use of anthrax vaccine, which enabled farmers in the pest-ridden sections to keep cattle with impunity, illustrates the value of this work to

2. Salmon: *Foot-and-Mouth Disease*, Year-Book, Dept. Agric., 1902, p. 643; Pearson: Circular No. 15, State Live Stock Sanitary Board of Pennsylvania, 1908.

3. Hamilton: *Louis Pasteur, His Life and Labors*, 1885, p. 238, D. Appleton and Company.

4. Chester: *Anthrax Bacteriologic Work*, Rep. Delaware Agric. Exper. Station, 1895, p. 64.

American agriculturists. The more recent method of vaccination, involving but one injection of virus with a quantity of immune serum, described by Sobernheim⁵ and used extensively in South America, is reported to have given excellent results. This means the saving of many animals.

In 1894 Chamberland⁶ reported that a total of 1,988,677 animals had been inoculated in France, and the loss from anthrax had diminished from 10 per cent. in sheep, and 5 per cent. in cattle, to less than 1 per cent. in sheep and 0.25 per cent. in cattle, a saving of over \$2,000,000.

Anthrax has been carried to many places in the United States, and were it not for the preventive measures that are being applied wherever it appears it would soon become a serious menace to the dairy and cattle industries of our country. This is illustrated by the outbreaks in northern New York, where in 1906 it appeared on eighty-four farms.⁷ There were 170 fatal cases before immunization by vaccination could be established. More than 3,000 animals were vaccinated and the ravages of the disease were stopped. Animal vaccination since that time has kept the disease in subjugation.

The number of animals that are necessary in the preparation and testing of the vaccine and in making early and positive diagnoses is not large, but the number of deaths and the amount of suffering prevented are great. So thoroughly familiar are our people with the fact that there is a preventive treatment for anthrax that it forms a part not only of their basic knowledge, but also of their working methods in protecting their flocks and herds.

CONTAGIOUS PLEUROPNEUMONIA OF CATTLE

This disease is said to have originated in the highlands of central Europe, whence it spread to every cattle-raising country in the world. It was estimated that during the first quarter of the nineteenth century this disease cost England \$450,000,000 in deaths alone. The additional losses for deterioration were never estimated.⁸

5. Sobernheim: Ueber das Milzbrandserum und seine praktische Anwendung, Deutsch. med. Wchnschr., 1904, Nos. 26 and 27.

6. Chamberland: Jour. d'Agric. prat., 1894, i, 627.

7. Burnett: The Control of an Outbreak of Anthrax, Am. Vet. Rev., 1908, xxxiii, 136.

8. Special Rep. No. 12, Dept. Agric., Washington, D. C., 1879, p. 233.

It was probably introduced into the United States in 1843, in a cow imported directly from Europe and taken from shipboard into a Brooklyn cattle-shed. At first its spread was not rapid, several years elapsing before it became widely disseminated in the Atlantic states. It was not, in fact, until about 1880 that it became evident to those most familiar with the disease that if it were not eradicated it would, through some one of the increasing number of avenues of transportation, soon reach the cattle ranges of the West and ruin the cattle industry of this country.

The general dissemination of this disease was due to the ignorance of the people concerning its contagiousness. In 1851 experiments⁹ at Pomeraye and other places in France demonstrated its infectious nature and showed beyond doubt that it would spread from diseased to healthy animals. Owing to general skepticism, these results were not accepted until they had been many times repeated. This was particularly true in the United States. The American mind wanted additional evidence and the result was the well-known experiments made by Dr. D. E. Salmon¹⁰ in 1884 on Barren Island. These furnished such undoubted evidence of the infectious nature of the disease that it was not difficult to obtain from Congress the necessary legislation and appropriation for instituting methods for its complete eradication. As a result every trace of this disease was removed from the United States¹¹ within the brief period of less than six years at a cost (\$1,509,000.72) that was trifling in comparison with the losses likely to occur annually as soon as the disease had obtained a foothold among the cattle on the western plains.

GLANDERS

This is one of the oldest equine diseases known. The ancients describe it and speak of the extensive losses it produced. Many theories existed concerning its source, the most prevalent one being its transmission in some unknown way through the air. Toward the end of the eighteenth century it was demonstrated by animal experiment that the disease was transmissible by inocu-

9. The report of the scientific commission appointed to make these investigations is translated in the Veterinarian, 1854, xxii, Series 3, vii, 335.

10. First Annual Report, Bureau of Animal Industry, U. S. Dept. Agric., 1885, p. 170.

11. Rusk, J. M., Sec. of Agric.: Proclamation, Eradication of Pleuropneumonia, Sept. 26, 1892.

lation and communicable to man. In 1882 its specific organism was discovered. It is hard for us to appreciate at this time the difficulty experienced in establishing the infectiousness of this disease, notwithstanding the enormous losses it was causing annually. Skepticism died out, however, when Loeffler and Schütz¹² were able to produce it with pure cultures of the bacillus they had discovered and, further, were able to show how its virus was disseminated through the nasal discharges from infected to well horses. Another victory was realized in the production of mallein from cultures of the glanders bacillus. By the use of this substance the disease can be detected in animals that have been exposed but which as yet do not show evidence of infection. By detecting and removing the infected horses before the disease comes in evidence and before the bacteria are escaping, the spread of the disease is checked. Glanders, like anthrax, is transmissible to man, and already a number of cases have been reported in men who have had the care of horses. Since the introduction of mallein and the enforcement of sanitary regulations compelling the destruction or isolation of infected animals, the spread of glanders has been greatly reduced. While general statistics are wanting, the importance of this disease can be understood from the fact that in ten years (1876-1886) in Prussia alone it destroyed 20,566 horses.¹³

In the United States glanders is of much significance, especially in the cities. Its early diagnosis and control are of great economic as well as sanitary importance. The methods by which to accomplish these results are the direct outcome of painstaking studies and experiments with animals.

RABIES OR HYDROPHOBIA

Among the diseases of man, none are more dreaded and in animals few are more pitiful than rabies. There is no longer any disagreement among pathologists as to the existence and dangerous nature of this disease or as to its being readily communicated from rabid to healthy animals. In the maladies heretofore cited, with the exception of contagious pleuropneumonia, the specific organism has been found, isolated and cultivated on arti-

12. Loeffler and Schütz: The Bacillus of Glanders, *Deutsch. med. Wchnschr.*, December, 1882; transl. in *Micro-organisms in Disease*, New Sydenham Society, 1886, p. 388.

13. Friedberger and Fröhner: *Therapie der Haustiere im Lehrbuch der speziellen Pathologie*, 1908, ii, 435.

ficial media. In rabies the search for the specific agent was unsuccessful for many years. The bodies discovered by Negri in 1903 are thought by many to be the cause. Prior to Negri's observations, however, the experiments in preventive treatment had become successful. The fact was established by experiments that when rabbits are inoculated with a bit of the spinal cord or brain of a rabid dog or other animal they will die after a certain length of time (usually from fifteen to thirty days) with definite and characteristic symptoms, and that when rabbits are inoculated by the same method with the spinal cord or brain of healthy dogs they will remain well. In 1884 Pasteur¹⁴ made the brilliant demonstration of his method of conferring immunity against rabies or hydrophobia before a commission of scientific men appointed to make an investigation into its merits. Concerning his first inoculation in man, Pasteur wrote:

Making use of this method, I had already made fifty dogs of various races and ages immune to rabies, and had not met with a single failure, when on July 6, quite unexpectedly, three persons, residents of Alsace, presented themselves at my laboratory. One of these, a boy of 9 years, who had been bitten in fourteen different places by a rabid dog, was saved.

At the Pasteur Institute in Paris, 9,433 persons were treated during the years 1886 to 1890 inclusive. The total mortality among those treated was 0.61 per cent. In 1890, 416 persons were bitten by dogs proved to be rabid, and among these there was not a single death. In 1891, the number of persons treated was 1,539, with a mortality of 0.25 per cent., and, in 1893, 1,790 inoculations were made with a mortality of 0.22 per cent.

Rabies has spread extensively in the United States during recent years. In 1908 there were reported in the registration area 111 deaths in man and 534 localities infected with rabies. There were nearly 1,500 people who took the Pasteur treatment for this disease.¹⁵ In 1908 there were 1,168 positive examinations¹⁵ for diagnosis of rabies in animals made in the United States. At the New York State Veterinary College from 1899 to 1908 a total of 496¹⁶ examinations for rabies in animals were made. These have all come from the rural districts and the smaller cities of the state. The exami-

14. Vallery-Radot: *The Life of Louis Pasteur.* ii, 219-290.

15. Kerr and Stimson: *The Prevalence of Rabies in the United States,* U. S. P. H. and M.-H. S., 1909, p. 7.

16. Moore: *Am. Vet. Rev.*, 1909, xxxi, 20.

nations in New York City are made at the laboratory of the City Board of Health. Of these 496 examinations, 424 were in dogs, the others in cattle, horses, sheep and hogs. The number of examinations is increasing, there being over 400 for the first ten months of this year. In Wisconsin¹⁵ 584 animals died of rabies during the past year. Of these, 100 were hogs, 400 cattle, 28 sheep and 56 horses. These facts are mentioned to show the significance of the disease for our domesticated animals.

The Pasteur treatment has been made so effective and inexpensive, as compared with former times, that, when desired, animals bitten by rabid dogs may be treated. The material may be sent from the laboratory where made, as from the New York City research laboratory for instance, and administered by the local veterinarian. The result of the work along these lines has not only proved to be a great blessing to humanity, but also a source of great relief to many animals. As a result of the fact that the method of dissemination of rabies has been determined, quarantine and other precautionary measures are possible to greatly lessen the number of animals infected.

SWINE DISEASES

The important infectious diseases of swine known to occur in the United States are hog cholera and swine plague. The first recorded epizootic of hog cholera in this country occurred in Ohio in 1833. It gradually spread until it became a menace to this branch of animal industry. In 1899 de Schweinitz estimated that the losses from this disease alone in the State of Iowa was \$15,000,000 annually. In other words, a disease supposed to have been introduced from Great Britain about 1830 had become a general and unquestioned plague by 1870. In 1903 de Schweinitz¹⁷ found that in the blood of hogs suffering from epizootic hog cholera there was a virus that would pass through a Berkefeld filter. Continued investigations in the Bureau of Animal Industry¹⁸ and elsewhere¹⁹ showed that swine could be immunized against this disease by the use of serum of hyperimmunized pigs. The result of this discovery has led several states to manufacture this serum for the

17. de Schweinitz: Cir. 14, Bureau of Animal Industry, Dept. Agric., 1903.

18. Dorset, Bolton and McBryde: Bull. 72 and 102, Bureau of Animal Industry, Dept. Agric.

19. King: Bull. 157, Kansas State Agric. Coll; Reynolds: Bull. 113, Univ. Minn. Agric. Exper. Station.

purpose of immunizing hogs. The saving from suffering and death to swine and the gain to the pork industry of this country resulting from this work is enormous. No one who has witnessed the suffering of hogs in outbreaks of a chronic type of hog cholera can fail to appreciate the great blessing that has come to this species of animals by bringing this scourge under control.

TEXAS OR SOUTHERN CATTLE FEVER

This disease, which has been called bovine malaria, has been known for many years in the South. It frequently gained entrance to the Northern states, where it caused heavy losses in the death of cattle. The following statement concerning the disease, which illustrates its mysterious nature as viewed in that time, is taken from Dr. Smith's report:

It was also discovered that southern cattle, after remaining for a short time on northern pastures, lost, in some mysterious way, the power to infect other pastures and were, for the remainder of their stay in the north, harmless. Again, cattle driven over a considerable distance lost, after a time on their way, the power to infect pastures. When pastures and trails had been passed over by southern cattle, it was observed that the disease did not appear at once in the northern cattle grazing on them, but that a certain period of not less than thirty days elapsed before the native cattle began to die. More curious than even these facts was the quite unanimous testimony of the stock-owners who had had more or less experience with this disease, that native susceptible animals did not transmit the disease to other natives, and that they were harmless.

In 1868, Texan cattle shipped up the Mississippi River to Cairo and thence by rail into Illinois and Indiana early in June caused during the summer of that year enormous losses of cattle in those states. Moreover, the east began to be aroused because western cattle infected with the disease had been shipped eastward for beef and were dying of Texas fever on the way, in the New York stock-yards, and elsewhere. The question as to the effect of such diseased flesh on human health was at that time entirely new and caused much uneasiness. The cattle commissioners of New York state and the Board of Health of New York City made a vigorous effort to check the importation of diseased cattle from the west, and to their effort we owe much valuable information of this disease.

By means of a careful series of experiments begun in 1889 Smith²⁰ found the cause of this disease to be a

20. Smith and Kilbourn: Bull. 1, Bureau of Animal Industry, U. S. Dept. Agric., 1893.

protozoon closely allied, if not identical, with the one discovered by Babes as the cause of a disease of cattle in Roumania, and that this organism was transmitted from the infected to the well cattle by means of the cattle-tick.

It has been repeatedly demonstrated by animal experiments that the cattle-tick is the carrier of the virus, and that in the absence of this tick Southern cattle can be shipped North at any time of the year with perfect safety to Northern stock, and that if ticks are removed from the pastures Northern cattle can live in the South. As the carrier of the virus is known, the disease can be prevented.

The discovery of the cause of this affection and its method of dissemination has led to most important results. Several of the Southern states²¹ have introduced methods of immunizing Northern cattle that were shipped into the South for breeding purposes, and more recently the government has undertaken to eliminate the cattle-ticks, thereby eradicating the disease. The value of the experiments which made possible these results to the live-stock industry, and which cost but a small number of animals, cannot be estimated, either in dollars or in the suffering of thousands of cattle they have saved.

TUBERCULOSIS

Of the diseases of cattle there is perhaps no other that causes as heavy losses as tuberculosis. This affection was known in very early times, but its means of spreading was very limited owing to the small traffic in cattle. In the nineteenth century it had become, however, a source of great loss, largely because the people did not know its cause or how it was spread.

In 1865 Villemin²² demonstrated, by inoculating healthy animals with tuberculous tissue, that tuberculosis was a 'communicable disease. In 1882 Robert Koch,²³ after repeated experiments on animals, discovered and isolated its specific organism. But for these

21. Francis and Connaway: Bull. 35, Texas Agric. Exper. Station, 1899; Connaway: Bull. 37, Missouri State Board of Agric., 1897; Dalrymple, Nirrgan and Dodson: Bull. 51, Louisiana Agric. Exper. Station, 1898.

22. Quoted by Hutyra and Marek: Spezielle Pathologie und Therapie der Haustiere, i, 472; original article by Villemin in Bull. Acad. Sc., Paris (1865-6).

23. Koch: The Etiology of Tuberculosis, Mitt. a. d. Gsndhtsamte, 1884, ii; Tr. New Sydenham Soc., 1886, p. 67.

and similar experiments, we should still be totally in the dark as to the cause of this disease and unaware of its communicability from animal to animal, or from animal to man.

The importance of these discoveries is too great for ready comprehension. Tuberculosis, while not characterized as an epidemic or epizootic disease, is estimated to be the cause of 14 per cent. of all the deaths in the human family, while from the post-mortem examination of the cattle slaughtered in the abattoirs of ten foreign cities and countries²⁴ cattle averaging nearly 18 per cent. have been reported to be tuberculous. In the United States it is estimated that probably 10 per cent. of the dairy cattle in the country are affected with tuberculosis. Dr. Melvin estimates further, on carefully collected data, that tuberculosis of food animals costs this country \$14,000,000 annually. Several herds have come to my notice in which on post-mortem examination from 75 to 90 per cent. of the animals were found to be diseased.

In order to determine the extent to which the disease has spread, I have collected and compiled the results of a number of tests made during the last two or three years, but largely in 1907, by a considerable number of veterinarians to whom the New York State College furnished tuberculin. The results show that of 421 herds tested 302 contained reacting animals.²⁵ These herds contained a total of 9,633 animals, of which 3,432 reacted. The official tests by the New York Department of Agriculture for the years 1904-6 inclusive, kindly furnished me by Dr. Kelly, include 262 herds with a total of 3,088 animals, of which 673 reacted. They were distributed in fifty counties. These herds all came under the operation of the law. Infected animals were found in one hundred and twenty-one herds.

Sanitarians have recognized the danger of human infection from the consumption of milk from tuberculous cows, and the presence of much tuberculosis in pigs and calves fed on such milk is a practical demonstra-

24. Statistics Collected by Freeman: Med. Rec., March 28, 1896. p. 433. In detail they are: Berlin 4.57, Munich 2.44, Augsburg 2.44, Mulhausen 3.4, Hanover 60 to 70, France 5, Paris 6, Holland 20, Pomerania 50, Mexico 34 per cent.

25. Melvin: The Economic Importance of Tuberculosis of Food-Producing Animals, Proc. Sixth Internat. Cong. on Tuberc., 1908, iv, 504.

26. Moore: Bull. 250, Cornell Univ. Agric. Exper. Station, 1908, p. 286.

tion of the transmission of the virus through this medium. The conclusion by many investigators is that from 1 to 2 per cent. of human tuberculosis, especially the glandular form, is of bovine origin.²⁷

There is a large literature on this subject. The report of the Royal Commission on Tuberculosis and the Proceedings of the Sixth International Congress on Tuberculosis are especially recommended for information on the transmission of bovine tuberculosis to man.

The cause of this disease, the manner of its dissemination, and the means (tuberculin test) by which it can be detected in its early stages, have been discovered by animal experimentation. The remaining step is to determine the best method for the elimination of the diseased animals. When this is ascertained, and the existing centers of infection removed, the enormous losses now annually sustained by deaths from this malady ought practically all to be averted. Judging from the known facts, it is highly probable that if attention had not been called to this disease in cattle, and a method for its early detection discovered, it would have become a more universal and destructive plague of cattle than any other that has yet visited the animal kingdom.

OTHER DISEASES

There are still other diseases of an epizootic nature that are worthy of mention and also those frequently of great local interest, which have been investigated by means of animal experimentation and robbed of much of their former terror. Blackleg and tetanus or lockjaw are prominent among these. Further, there are the animal parasitic diseases, such as trichina in pork, fluke diseases of cattle and sheep, and the tapeworm diseases of sheep. A nodular disease of the intestines of sheep²⁸ due to a small round-worm and one in fowls²⁹ due to a tapeworm were once supposed to be tuberculosis, and in the effort to eradicate them many animals were sacrificed. A disease in cattle known as the cornstalk disease, which was thought, especially in Europe, to be contagious and therefore requiring rigid quarantine, has been shown to be due to local causes and in no way trans-

27. Smith: Med. News, New York, 1902, lxxx, 343; Tr. Massachusetts Med. Soc., 1907.

28. Curtice: Animal Parasites of Sheep, U. S. Dept. Agric., 1890, p. 165.

29. Moore: Circ. 3, Bureau of Animal Industry, U. S. Dept. Agric., 1895.

missible from one animal to another.³⁰ Surra³¹ was recently kept out of this country, although it was brought to our shores, because a diagnosis was possible by means of animal inoculation. Much light has been shed on the infectious diseases of poultry, such as "blackhead" in turkeys and diphtheria and tuberculosis in chickens. A new disease of fowls, a filth disease, which is frequently called fowl cholera, has been discovered and can be prevented by the adoption of a régime of cleanliness, wholesome food and ventilation. Recently Mohler has identified a serious disease of sheep, which affects the lips and legs and which was thought to be foot-and-mouth disease, as an infection with the bacillus of necrosis. While it is of much local concern, the animal inoculations proved that it was not the much-dreaded epizootic foot-and-mouth disease. Attention should also be called to the great importance of animal investigations now in progress on various serums, toxins and antitoxins, for the purpose of securing efficient remedies for the various infectious and epizootic diseases.

In zootechny, or experimentation for improving breeds of domesticated animals, the investigations have been of unquestioned importance to the agriculturists. Whatever the views on breeding may be, no one doubts for a moment that the modern breeds of farm animals are a great improvement over the original and native stock. While the natural resistance of these animals against infectious diseases may have been appreciably lessened from that of the native stock, the knowledge we possess of how to keep these diseases away from our flocks should encourage future experimentation for the purpose of raising better and swifter horses; cows to give more and richer milk; sheep to yield finer wool and more of it; and swine to grow more pork per bushel of corn.

FURTHER INVESTIGATIONS NECESSARY

A study of the efforts which have been made for the suppression of infectious diseases of animals both in this country and abroad shows that, while wonderful advances have been made, the desired results in many instances have not been fully attained. There are those

30. Moore: Bull. 10, Bureau of Animal Industry, U. S. Dept. Agric., 1896; Mayo: Bull. 49, Kansas Agric. Exper. Station, 1895.

31. Mohler: 24th Annual Report B. A. I., U. S. Dept. Agric., 1907, p. 34.

who, ignorant of what has been done, and equally ignorant of what there remains to do, question the necessity for further investigations. Great as have been the achievements in the past, it must be evident to every well-informed and unprejudiced mind that still greater achievement—greater whether measured by relief of suffering or by financial gain—are within reach in the near future. The benefits to agriculture and mankind in general which have accrued from the investigations of the past are no nearer their maximum limits of success than was the practical application of steam when Fulton built his first steamboat. Knowledge of the diseases of animals made little growth until the development, by means of repeated experiments on animals, of the newer pathology, which tends to reveal the nature of these affections, thereby pointing to methods for their control. In spite of all that has been done, practical preventive medicine has barely passed its infancy, and the important investigations into the so-called general diseases and dietary disorders have hardly begun.

The demands for further investigations were never more pressing than they are to-day. If they are checked we shall experience in this country what Great Britain has already suffered. Owing to a crusade which finally found expression in a parliamentary enactment, animal experimentation has been so crippled in Great Britain that the country which should have done the most by virtue of her wide geographical possessions and vast live-stock interests for the improvement of methods of preventing and controlling infectious diseases, has done practically nothing. I quote from one of England's foremost veterinarians³² in a plea for animal experimentation:

No country in Europe has, possibly, sustained greater loss during the last thirty-five years than our own; yet no country, perhaps, should have suffered less. With the finest breed of horses, and the most magnificent herds and flocks in the world, and a teeming population, whose health and wealth are largely centered in these, we have entirely neglected to protect them from the ravages of disease of home and foreign origin, by forgetting to foster and encourage that science which alone can accomplish this. That neglect has cost Great Britain and her colonies untold millions.

32. Fleming, George: *The Contagious Diseases of Animals; Their Influence on the Wealth and Health of the Nation, and How They are to be Combated.*

Furthermore, experiments which have demonstrated important facts to us are not always accepted by others unless they can be and are verified. There is in human nature an inherent demand for visible proof. In order not to retard progress, it is often necessary that the doubting Thomases should be convinced, and the only way to accomplish this is by repeating what has already been done. This is always necessary in teaching those who are to continue the work of controlling animal diseases. In other words, a certain amount of experimentation must be carried on as a means of education.

In the practice of veterinary medicine and veterinary sanitary science, it is often necessary, for purpose of diagnosis, to make inoculations immediately. At such times every hour of delay may mean the death of many animals. In charity to dumb creation itself, therefore, there should be no restrictions to delay the work.

In order to make diagnoses, to prepare vaccines and antitoxins with which to better the conditions of animals, it is necessary that animal experimentation be continued. It is the only humane thing to do. If this work were checked, it would entail a vast amount of needless suffering on animals exposed to the various infections, and threaten the prosperity of the animal industry of the country. To spare the very few experimental animals necessary in procuring life-saving results would require annually the sacrifice of tens of thousands of other and more valuable animals to all sorts of infectious diseases. The time has come when every humane individual must protest against interference with animal experimentation.

Most animal experimentation does not inflict great suffering. Anesthetics are freely used, and experimenters do not permit unnecessary pain. In most cases the animals used in experimentation have a more comfortable life and a far easier death than those that have the freedom of nature and allowed to perish by the so-called natural disease. Those who have witnessed the prolonged suffering endured by large numbers of wild animals that die from chronic diseases will verify this statement. The pain inflicted in those experiments in which anesthetics cannot be administered is not usually greater, and is often much less, than that resulting from the violent death experienced by many animals in their natural surroundings. No one who has observed the suffering of

animals while they are dying with one of their many natural diseases, or because of the cruelty of beasts of prey, can feel that animal experimentation, as practiced in recent years, imposes as cruel a death as do the unalterable laws of Nature. The objectionable vivisection practiced in earlier days in veterinary colleges no longer exists.

When, therefore, the subject of animal experimentation is considered broadly, and in the light of natural laws which give a limited life period and certain death to every individual, it resolves itself into the simple question: Shall the lives of a few animals be shortened because of experimentation? Men and women are allowed wantonly to shoot and trap innocent animals and birds simply to gratify an appetite for brutal pleasure, or to procure furs and plumes for adornment and use. We permit unlimited slaughter of young animals for human food; why, then, should we hesitate to shorten the lives of a few that thousands of others may be protected from disease and suffering? The investigations involving animal experimentation have the broadest economic and humanitarian value, and they should not be retarded by misguided sentimentalism.

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The History, Prevalence and Prevention of Rabies and Its Relation to Animal Experimentation

"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—Charles W. Eliot.

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BOSTON

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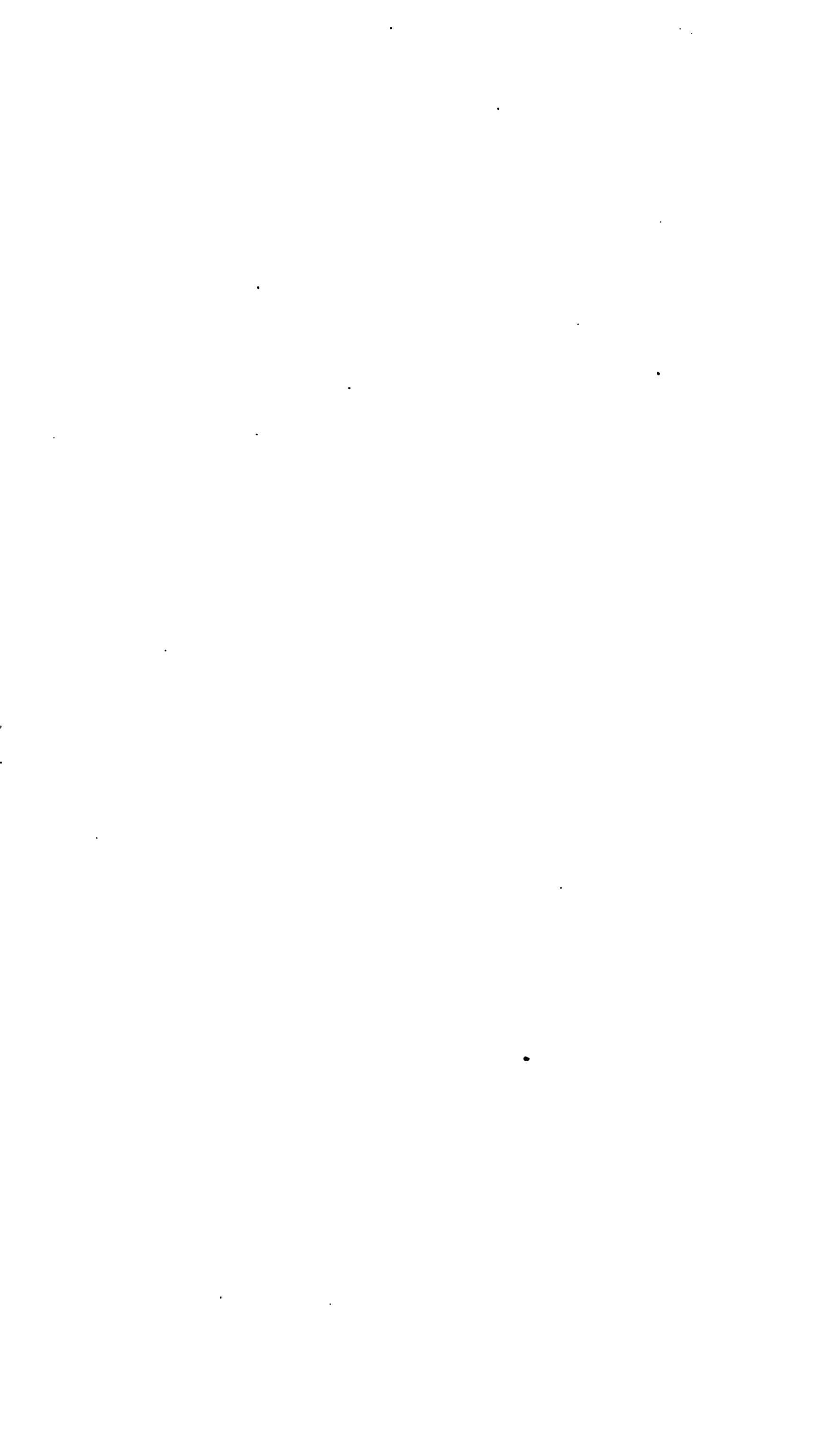
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BOSTON



THE HISTORY, PREVALENCE AND PREVENTION OF RABIES AND ITS RELATION TO ANIMAL EXPERIMENTATION

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BOSTON

One cold, stormy, January night a poor, weather-beaten, tired and bedraggled dog appeared at a farmhouse some twenty miles from Boston. He had evidently traveled a long road and was sheltered and fed and treated with the usual kindness that any one with a heart in him would show to such a waif. The next morning he "made friends" with the neighbor's dog Pete, and, dog-like, the two exchanged a few bites in the process. During the day he seemed morose and unfriendly, and snapped at people, and, from a fear that he might bite the children, he was shut up in an out-building. The next morning he was found dead.

In February the neighbor's dog made a vicious attempt to bite a horse driving into the yard. Amazed at such unusual conduct, the farmer drove the dog away with a whip, and the animal disappeared down the road, never to be heard from again except that an animal answering his description was seen to attack two puppies in the near-by village. These two puppies died a few weeks later with symptoms of rabies.

It was Pete's custom to sleep in the barn; and in March two cows in this barn, and a week later two more cows, died showing unmistakable symptoms of rabies, in the opinion of a veterinarian in the employ of the State, who has had much experience with this extraordinary disease.

The explanation was simple: the poor waif had been suffering from rabies, his friendly (?) bite had infected Pete, who had in turn bitten the pups and the cows, and

all had died of rabies.¹ There had been no rabies in or about this town before the advent of this waif.

Such strange tales as this, and more strange, were told by our fathers and by their fathers, and each generation back through the centuries has no doubt heard similar stories; and, if we go back as far as the fourth century before the Christian era we find the first record of this disease in the words of Aristotle: "Dogs suffer from madness that puts them in a state of fury, and all animals which they bite, when in this condition, become also attacked by madness."

And, if we return through the ages, following the literature, we find reference to rabies in the works of Virgil, Horace, Ovid and Plutarch. The disease in human beings was first recorded by Cornelius Celsus in the first century A. D., who was also the first to use the word "hydrophobia." Dioscorides recommended the extirpation of the wound as protection against the disease, and Galen in the second century A. D. stated special remedies for rabies. Furthermore, Pliny the younger, Columella and C. Aurelianus may be mentioned among the early authors who referred to the disease. Nothing comes to us on the subject from the middle ages. In 1591 Bauhin in his "*Memorabilis historia luporum aliquot rabidorum*" speaks of the infection of human beings by rabid wolves. There was an epizootic of rabies in 1604 in Paris (Andry); toward the end of the seventeenth century in Italy (Baglio, Rammazzini); in 1708 in Suabia;² in 1719-23 in France and Germany; in 1754-1760 in England; in 1779-1807 in America, especially in West Indian Islands and Peru. Toward the end of the eighteenth and the beginning of the nineteenth century rabies had spread all over Europe. From 1803 to 1830 there was an epizootic of rabies among the foxes in Southern Germany and Switzerland (Köchlin and Franque). The saliva of the rabid dog was demonstrated by inoculation experiments to be infectious by Zinke (1804) and Gruner and Salm (1813); that of herbivora by Berndt (1822), and that of human beings by Magendie.

1. To prove the matter beyond peradventure, the brain of the waif (still in fair condition owing to the cold weather) and one of the cows were sent to me for examination, and Negri bodies were easily demonstrated, proving the disease to have been rabies.

2. Camerarius and Scharff: *Dissertatio inaugural de Alysso clave, Tübingen.*

In 1814 and 1815 accurate experimental investigations regarding the disease were made by Viborg in Copenhagen and Waldinger in Vienna. The clinical knowledge was especially enriched in 1817 and 1818 by Delabère-Blaine and Greve (England). In 1822 the epizootic prevailed in Holland, in 1823-1824 in Berlin and Prussia, in 1824 in Sweden and Russia. During the outbreak from 1823 to 1830 Hertwig published³ a large number of carefully carried-out inoculation experiments on animals which greatly advanced our knowledge. Virchow showed the fallacy of the spontaneous origin theory in 1854.

Galtier of the Lyons veterinary school gave us a method of transmitting the disease to rabbits, thus establishing the often necessary proof that a given suspicious case was truly one of rabies. He also made experiments to confer immunity with saliva and brain matter (1880-1881). The marvelous researches of Pasteur and his coworkers Roux, Chamberland and Thuillier (1881-1889) demonstrated the location of the purest and most concentrated virus in the central nervous system and gave to the world the wonderful protective inoculation which has reduced the mortality in man to a fraction of 1 per cent.

It was imperative that these investigators should use in their studies many animals, and those of different kinds, or no advance in knowledge would have been made. Animal experimentation always has been and always will be absolutely necessary to acquire accurate knowledge of any infectious disease, regarding its cause, means of dissemination, lesions produced, treatment and methods of prevention and eradication.

With the hope of being able to discontinue the necessity of inoculating animals (usually rabbits or guinea-pigs) in order to prove the existence of rabies in a given suspicious case, investigators have endeavored to find definite microscopic evidence equally reliable. Great advances in this direction were made by Van Gehuchten and Nelis in 1900 and by Babes at about the same time by their discovery of characteristic cellular lesions occurring with much regularity in certain portions of the central nervous system of animals and people that had died of rabies, but, as these lesions cannot be consid-

3. Hertwig: Beiträge zur näheren Kenntnis der Wuthrankheit, 1828.

ered specific—there being a possible error of perhaps 2 per cent.—animal inoculations were still necessary in most instances. Since 1903, however, they have been rendered much less necessary by the discovery by Negri of very definite microscopic “bodies” in the nerve-cells of various portions of the brain in cases of rabies. In these bodies, which bear the name of the discoverer, we are probably close to the long-sought cause of rabies, and their presence having been demonstrated in a given case it no longer seems necessary to resort to animal inoculation to establish the existence of the disease.

As before stated, the disease had become widely spread over Europe during the early part of the nineteenth century. So we read of outbreaks continuing in 1838-40 in Austria and Württemberg, and in 1852-3 in Prussia. For example, in the last-mentioned year 150 rabid dogs were brought to the Berlin Veterinary School, and in Hamburg there were 267 cases of rabies. In 1861 there was an epizootic in the Rhine provinces and France; in 1863-1871 in Württemberg; in 1862-1867 and 1873-1876 in Vienna; in 1865-1866 in Saxony; in 1871-1876 in Saxony, Bavaria and Prussia. Since the introduction of proper dog laws and compulsory muzzling the disease has greatly diminished in most of the German states, a yearly average of about 700 rabid animals being reported from 1866 to 1902,⁴ usually near the border line of countries where muzzling is not enforced.⁵ With such laws Denmark, Sweden and Norway have not known rabies for more than fifty years, and it has recently been eradicated from England and Switzerland. It has never been known in Australia, probably owing to the strict enforcement of a six months' quarantine for dogs.

With the exceptions noted, practically every European country—France, Austria, Hungary, Belgium, Holland and Italy—shows a record somewhat similar to that of Germany. Russia has had years of experience with this disease, and that country and Austria constantly supply the German towns on their borders with fresh cases. Roumania, Servia, Bulgaria and Turkey are by no means free, although the fact that dogs in the latter country suffer more often from “dumb” rabies explains the re-

4. Friedberger and Frohner: *Spezielle Pathologie und Therapie der Haustiere*, 1904, ii, 548.

5. See maps, etc., in Kitt's *Was muss jeder Hundebesitzer wissen?* Stuttgart, 1908.

son why it is not wider-spread in that land.⁶ Rabies is also frequently reported in Africa and Asia.

It is naturally the pride of health boards and of governments to show as little disease as possible in their respective communities, and it is doubtless always with regret that they report outbreaks of infectious disease. Therefore, if official figures are to be misrepresented, they would naturally be minimized rather than otherwise. We must consequently assume that, if the figures given for rabies and all other infectious diseases occurring in various lands are not true figures, they probably and undoubtedly represent fewer cases than actually occur, inasmuch as, unless remarkable supervision is exercised, numerous cases of disease are never reported, or escape detection.

In North America rabies exists in Canada, Mexico, Cuba and very widely in the United States. Accurate mortality statistics for all the states are impossible to obtain, as they are not kept with the same precision as in some European countries, nor has the prevalence of rabies in animals been recorded with much accuracy. We know, however, that it has existed here for about a century and a half. The first outbreak occurred in Boston in 1768, and in 1770 and 1771 it was observed in dogs and foxes in the same vicinity. It was reported in Philadelphia in 1779 and also in Maryland. In 1785 it was prevalent throughout the northern states and soon after spread to the southern states.⁷ Peters⁸ quotes from a Boston newspaper of 1798, which indicates that the disease existed in Rhode Island at that time, and there is little doubt that it has existed there and in many other states from time to time ever since. For example, it must have been prevalent in Massachusetts between 1876 and 1882, for during that period 44 people died of rabies, and again between 1888 and 1894 there must have been another outbreak, for 45 people died of it dur-

6. Remlinger and Mustapha-Effendi, Hutyra and Marek : Spezielle Pathologie und Therapie der Haustiere, 1909, i, 467; Remlinger : Rabies in the Street Dogs of Constantinople, Jour. Tropical Veterinary Science, 1909, iv, 561. In this article Remlinger offers another explanation, not for the Ottoman Empire, but for the city of Constantinople. In closing he says: "It is in the special conditions under which street dogs live, in their distribution into distinct groups, in the subtle instinct which makes the others avoid a rabid dog, to which we must attribute, more than to any peculiarities in the disease itself, the rarity of rabies in Constantinople street dogs."

7. Moore : The Pathology of Infectious Diseases of Animals, 1906.

8. Peters : Am. Jour. Pub. Hyg., 1907, p. 96.

ing this period.⁹ The largest number of deaths in any one year was 17 in 1890; 15 in 1878, and 14 in 1877 and again in 1889. Previous to this the reports show that 28 people died of hydrophobia between 1842 and 1876, the number varying considerably with the years, often no deaths and once as many as 6 in 1854.

In Massachusetts vital statistics of this disease in animals began to be kept in 1895, and Table 1 is made from the reports of the Cattle Commission (now the Cattle Bureau), the Boston Board of Health, the State Board of Health, Massachusetts reports of births, marriages, deaths, etc., and from figures kindly given me by the Health Department of the City of New York and by Dr. Rambaud of the Pasteur Institute of New York.

TABLE 1.—RABIES IN MASSACHUSETTS

Year.	Mortality Dogs.	Mortality Other Animals.	Mortality People.	People Exposed and Given the Pasteur Treatment.
1895.....	4	0	0	11
1896.....	12	2	2	7
1897.....	19	8	0	8
1898.....	25	2	2	11
1899.....	1	1	0	3
1900.....	3	0	0	0
1901.....	11	0	0	1
1902.....	2	0	0	1
1903.....	1	1	0	1
1904.....	2	0	0	0
1905.....	98	5	2	12
1906.....	356	43	8	133
1907.....	741	37	2	165
1908.....	511	53	5	144

These figures are fairly accurate, although probably far too low, as there can be no doubt that many cases in animals, and men also, were never reported. Suspicious cases are not included in the above table; the figures represent only such cases as were demonstrated beyond all reasonable doubt to be actual cases of rabies, either by a clear history of a bite by a rabid dog and subsequent typical symptoms, by the presence of Negri bodies, by lesions in the Gasserian ganglia, by animal inoculation and often all of these proofs in sequence.

Many of our states would show a similar or a worse record if figures were obtainable, but they are difficult to secure.¹⁰ There is little doubt, however, that the disease is widely spread over the country, and few states, if any, are free from it.

9. Rep. Mass. State Board of Health.

10. Kerr, J. W., and Stimson, A. M.: The Prevalence of Rabies in the United States, THE JOURNAL A. M. A., Sept. 25, 1909, lxxii, 980.

Yet in spite of all historic and scientific evidence there are a few medical men who say they do not believe there is any such disease as rabies. They accept without remark other infectious diseases, but rabies is beyond their comprehension. If asked why they hold such contrary opinions, their usual reply is that they have never seen a case. Perhaps they have also not seen smallpox, glanders, trypanosomiasis or China, yet they do not deny their existence.

Here are two historic and scientific facts which have been demonstrated over and over again:

1. If ten persons are exposed to the same gonorrhreal infection, a varying per cent. will surely contract the disease, unless preventive measures are employed.

2. If a rabid dog bites ten persons, or animals, a varying per cent. will surely become rabid unless preventive measures are employed. And yet it is as difficult to convince the person who accepts the one and rejects the other as it is to convince the man who refuses to trust the scientific evidence that the earth is not flat.

It is often stated that Pasteur institutes do not prevent rabies, but cause it. They may, so far as they insure a very reliable protection against the disease and consequently induce a carelessness in enforcing proper dog laws which in themselves would be sufficient to stamp it out.

Pasteur institutes are of two kinds, public and private. Public Pasteur institutes are established by endowment, such as the Pasteur Institute in Paris; by governments such as those of the United States Public Health and Marine-Hospital Service at Washington, the New York City Board of Health and the Consejo Superior de Salubridad, Mexico City; by universities, such as the Pasteur Institute of the Universities of Moscow and Bucharest. These are founded for the benefit of the people of the country and for the study of this and other diseases. Private Pasteur institutes are what the name implies, but it is as unfair to impute ulterior motives to their proprietors as it is to assert that all physicians have but one end in view in the practice of their profession. Both do an immense amount of charitable work which is never made public, and for which they often receive not even a thank-you.

Pasteur institutes will cease to exist as soon as properly enforced dog laws eradicate rabies, for no infectious

disease can be so easily eradicated. It only needs the cooperation of humanitarians and real dog lovers to pass and enforce the necessary dog laws, and in a few years this will be accomplished. (See English statistics.)

The Pasteur preventive treatment has reduced the mortality of persons bitten by rabid animals from between 6 and 14 per cent. to a fraction of 1 per cent. The statistics of all the Pasteur institutes show this. No class of men is more ready to discredit the work of his brother, or is a more severe critic, than the scientist who controls the work of another, yet the statistics of all institutions giving the Pasteur treatment singularly agree. They may be read in the reports of the various governments and universities or in the *Annales de l'Institut Pasteur* from the time of the first publications by Pasteur.

A few tables will suffice to illustrate. To quote from Law:¹¹

The following table gives the number of individuals treated who had been bitten by animals which had been proved rabid by successful inoculation of other animals, and of those bitten by reputedly rabid animals, and their respective mortality:

	RABID, RESPECTIVELY	Died.	Mortality. %
Bitten by animals proved rabid by inoculation	2,872	20	0.69
Bitten by animals pronounced rabid by veterinarian	12,547	61	0.48
Bitten by animals suspected of rabies.	4,747	15	0.31
Average mortality			0.46

The Pasteur treatment by its great success in persons who have already been bitten has in a great measure robbed hydrophobia of its terrors, only it must be resorted to as early as possible in the period of incubation.

In this connection it should be remembered that there is no known cure for rabies when symptoms have once appeared and that death follows a train of well-recognized phenomena, agonizing to the sufferer; and the delirium and mania, the violent reflex spasms of mouth and larynx with inability to swallow, are harrowing to the observer no matter how extensive his experience as a forced witness of others' suffering. Physicians who have been so unfortunate as to see a person with hydrophobia

11. Law : Veterinary Medicine, 1900, iv, 331.

usually have no desire to see another, and find difficulty in eliminating the haunting recollection.

The figures of the Pasteur Institute of Paris,¹² 1886-1907, are given in Table 3.

TABLE 3.—FIGURES OF THE PASTEUR INSTITUTE OF PARIS,
1886-1907

Year.	Persons Treated.	Deaths.	Mortality. %
1886.....	2,671	25	0.94
1887.....	1,770	14	0.79
1888.....	1,622	9	0.55
1889.....	1,830	7	0.38
1890.....	1,540	5	0.32
1891.....	1,559	4	0.25
1892.....	1,790	4	0.22
1893.....	1,648	6	0.36
1894.....	1,387	7	0.50
1895.....	1,520	5	0.38
1896.....	1,308	4	0.30
1897.....	1,521	6	0.39
1898.....	1,465	3	0.20
1899.....	1,614	4	0.25
1900.....	1,420	4	0.28
1901.....	1,321	5	0.38
1902.....	1,005	2	0.18
1903.....	628	2	0.32
1904.....	755	3	0.39
1905.....	727	3	0.41
1906.....	772	1	0.13
1907.....	786	3	0.38

The figures in this table are similar to those of all the Pasteur institutes of the world, for example that of Tunis,¹³ where in 1906, 489 persons were treated, with no deaths. Since the foundation of this institute 2,490 persons have been treated, with 9 deaths, or a mortality of 0.36 per cent.

At the Pasteur Institute of the University of Bucharest, in 1903-1905, 3,091 persons were given the preventive treatment and none died.

In Berlin, in 1898-1902, 1,416 persons were given the Pasteur preventive treatment, of whom 12, that is 0.84 per cent., died of rabies, while among those not treated the mortality was 6.9 per cent. In Prussia during the year 1907, 281 persons were treated, of whom 4, that is 1.4 per cent., died of rabies, while of those not treated 2, that is 7.1 per cent., died.

At the Budapest Pasteur Institute in 1890-1907, 35,639 bitten persons received treatment, of whom 159, that is 0.44 per cent., died of rabies, while from 1890 to 1903, of 1,861 bitten persons not treated 266, that is 14.29 per cent., died of rabies.

12. Ann. de l'Inst. Pasteur, 1908, p. 557.

13. Bull. de l'Inst. Pasteur, 1907, p. 404.

In 1905 there were treated in forty Pasteur institutes in various parts of the world 104,347 people, of whom 560, that is 0.54 per cent., died of rabies later than fourteen days after treatment had ended. According to the location of the bite, i. e., whether on the head or the hands, the mortality of the treated varies from 1.99 to 0.36 per cent.¹⁴

The Pasteur preventive treatment depends on the fact that the spinal cord of a rabbit that has been inoculated with "fixed" virus and died of rabies in from six to seven days, loses its virulence day by day, so that at the end of fourteen days it is no longer capable of producing harmful effects.

Beginning, then, with an emulsion of a small piece of cord that is not virulent, or slightly so, the patient is inoculated daily for about twenty days with increasing strengths of the virus until his system has reacted to such a degree that it can withstand the stronger virus and immunity is produced. For this purpose many rabbits must be employed. Many rabbits and guinea-pigs must also be employed for the purpose of diagnosis in all laboratories where this work has to be done, such as laboratories of the boards of health, for instance. Happily, however, not so many animals must be used for this purpose as formerly, owing to the discovery of the Negri bodies. Unless the future develops some other method of diagnosis and treatment, this sacrifice of rabbits and guinea-pigs must continue until rabies is eradicated.

An article¹⁵ on hydrophobia which was recently sent to me was written, doubtless, with the hope of comforting many people and with the best intentions for the general welfare of the country. But I judge that the writer has had no personal experience with rabies and has spent little time on the study of the accepted scientific literature of this or any other infectious disease. Consequently many of her statements are not "facts," and if they are read by people who know nothing of medicine or medical literature, much real harm will be done instead of evidently intended good.

She would have us believe, for instance, that the Pasteur institutes are to a large extent responsible for hydrophobia, whereas it is the other way about; if there were

14. The above statistics are from Hutyra and Marek.

15. White, Caroline E.: Facts about Hydrophobia, Jour. Zoophily, May, 1909.

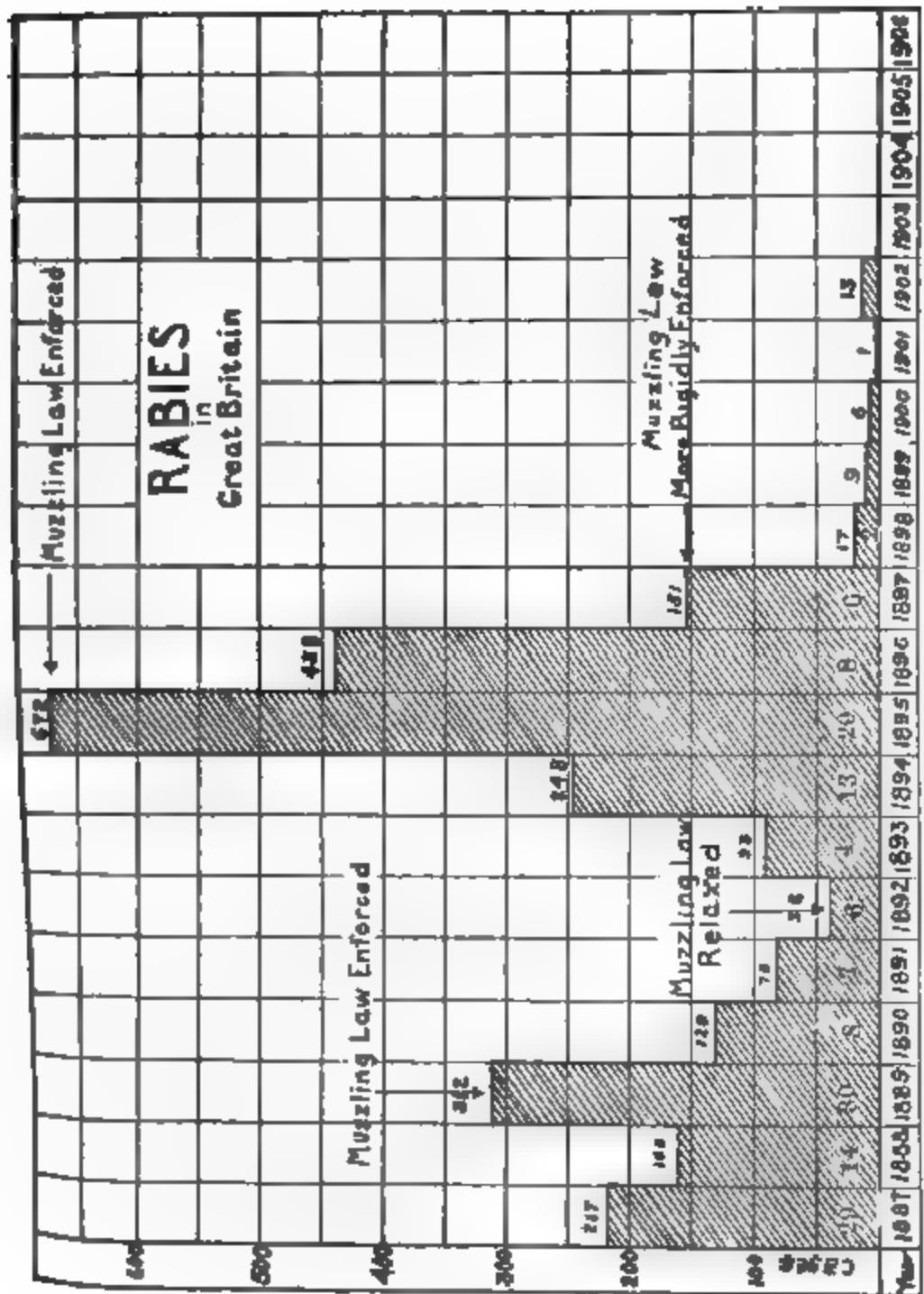


Chart showing relation of enforcement of muzzling law to prevalence of rabies in Great Britain. The figures in the cross-hatching indicate the number of persons who died of rabies in England. Credit for making this chart is largely due to Mr. Aubrey H. Strauss.

no rabies there would be no institutes, and certainly the disease is much older than the institutes. To quote (p. 47) : "In Germany, where there is scarcely any hydrophobia, they declined the offer of the Pasteur Institute." This is not a "fact," for there are two such establishments in Germany, the *Institut für Infektionskrankheiten*, Berlin, and the *Hygienische Institut*, Breslau; moreover there is still considerable rabies in that country, as we may see by referring to the works already mentioned, although now fewer deaths than formerly in human beings, perhaps largely owing to these very institutes.

Again to quote from this article :

In England hydrophobia is almost extinct. The report of the Registrar-General for Great Britain and Wales . . . in 1907 said that in 1906 and for three years previously there had not been a single case of hydrophobia in the United Kingdom, and this same United Kingdom refused to have a Pasteur Institute.

Nothing could be more misleading than this "fact." The true reason that there is no rabies in England has nothing whatever to do with Pasteur institutes; it is merely that proper dog laws were enforced, i. e., all unlicensed and unmuzzled dogs were destroyed, as also all dogs exposed to a rabid one. The accompanying chart compiled from the "Annual Reports of Proceedings under the Diseases of Animals Acts" explains the matter very simply.

This scheme is so readily grasped that explanation seems unnecessary. The number of cases of rabies here given refer only to the dog. Other animals are excluded, and I have only added the number of deaths in man to show how they rise and fall with the number in the dog. It should be remembered that many English people annually took the preventive treatment; for example, 147 in the year 1892. These are the only figures that I have, but, if so many took the treatment that year when so few dogs were reported, it is fair to assume that the number increased when more dogs were affected.

Note that in 1892 there were but 38 rabid dogs in England. At this time the authorities listened to a petition of "dog-lovers" and removed the "cruel muzzle," with the result that during the next five years 1,602 dogs, to say nothing of many other animals, and 51 peo-

ple died of the most agonizing disease known to the medical world. In spite of this fearful lesson these "humanitarians" came again in 1899 with another petition signed by 50,000 of them asking once more to be relieved of the annoyance of the muzzle. Fearing a repetition of the above calamity, the authorities wisely remained obdurate, with the result that in 1905 no case of rabies occurred in England, and there has been none since. The sudden rise to 13 cases in 1902 is very instructive. These cases occurred in a wild, hilly district of Wales where both people and dogs were difficult to control, but by rigid enforcement of the laws the trouble was stamped out.

The muzzles have been removed from the dogs in England, but will be resumed with the appearance of the first case of rabies. Moreover, there is a strict quarantine of six months imposed on any dog brought into the country.

Many people argue that the matter was comparatively simple in England, but similar results cannot be accomplished here, as this is not a "little island." This is true to a certain extent only. If, for instance, all dogs of a state were muzzled and a rabid dog should come over the boundary from a neighboring state and bite a number of dogs, a certain percentage of these dogs would certainly develop rabies if not destroyed, but the dogs of this given state being all muzzled, the disease would spread no further; in other words, it would be kept down to the minimum.

Even local muzzling may be of great value if properly enforced. For example, not long ago a rabid dog attacked a number of school children and bit several of them severely, necessitating their taking the Pasteur treatment. This dog ran from a neighboring town where a muzzling order existed at that time, and, had he been properly muzzled or immediately shot for not being so, this calamity could not have occurred. Many similar instances might be given.

Even inadequate muzzling sometimes does much good, for it may succeed in preventing an individual dog now and then from spreading this truly terrible disease.

If those opposed to animal experimentation in general and Pasteur institutes in particular are truly interested in preventing much suffering in both animals and man as far as rabies are concerned, they should devote their

energies to advocating the adoption of the historic methods employed in England and other countries for the suppression of this disease, and they will have the well-earned satisfaction of knowing that they have accomplished enormous good by assisting in the eradication of rabies from our country without any more annoyance to the dog than is daily experienced by all our draft animals in harness.

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The Importance of Animal Experimentation in the Development of Our Knowledge of Dysentery, Cholera and Typhoid Fever

MARK WYMAN RICHARDSON, M.D.
Secretary of the State Board of Health of Massachusetts
BOSTON

DEFENSE OF RESEARCH PAMPHLET VIII

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

—
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MARK WYMAN RICHARDSON, M.D.
Secretary of the State Board of Health of Massachusetts
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THE IMPORTANCE OF ANIMAL EXPERIMENTATION IN THE DEVELOPMENT OF OUR KNOWLEDGE OF DYSENTERY, CHOLERA AND TYPHOID FEVER

MARK WYMAN RICHARDSON, M.D.
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BOSTON

[EDITORIAL NOTE:—The following facts in relation to Dr. Richardson and his work will be of interest to the reader: Since 1896, Dr. Richardson has carried on almost continuously at the Massachusetts General Hospital research work connected with problems relating to typhoid fever. He was one of the first in this country to isolate the typhoid bacillus from the stools, urine and sputum, and first brought to the attention of the medical profession the value of hexamethylin in combating the bacilluria of typhoid fever. Later investigations have dealt with the treatment of typhoid fever with specific filtrates, serums, residues and vaccines and finally, through Dr. Richardson's efforts, antityphoid inoculation for the prevention of the disease has been introduced in ten training schools for nurses in Massachusetts.]

Before successful warfare can be waged against an infectious disease it is of the highest importance, if, indeed, it is not absolutely necessary, to know with precision the nature of the agent which produces that disease, how it invades the individual, what its method of action is, how it is excreted, and, finally, how it perpetuates itself outside the living body.

In studying the possible causes for any such infectious process, the suspected causative agents must be applied under strict scientific control either to members of the human or of the animal species to see whether under fixed conditions there is a definite relation between the suspected causes and the effects produced by them.

Typhoid fever, cholera and dysentery are diseases associated symptomatically and pathologically, in the great majority of instances, with the intestinal tract, and in the search for the causes of these diseases it was natural that study should focus itself on the rich bacterial flora of the intestines. This study, under the influence of new methods developed during the past twenty-five years, brought to light from the diseased intestines a great variety of living organisms, and the relation of any or all of these to the diseases under consideration offered a problem of the greatest complexity. To inoculate human beings with the various organisms found was manifestly impossible. Recourse to the use of the lower animals, therefore, had to be taken, and in the pursuit of knowledge concerning these diseases many thousands of animals have, undoubtedly, been sacrificed. It was found early, however, that, though many of the intestinal germs caused sickness and even death in the animals used, a clinical picture characterized by symptoms relative to the intestinal tract was rarely produced. An important link, therefore, in the chain of evidence connecting the germ with the human disease was lacking.

In the early nineties, however, an important discovery was made by R. Pfeiffer—a discovery which has in many ways revolutionized our knowledge of bacterial disease.¹ Pfeiffer found that by inoculating guinea-pigs and rabbits with gradually increasing numbers of different races of bacteria, he could at last bring the animals to a state in which they could stand without symptoms doses which, at first, would have proved fatal. In other words, the animals had become immune. In fact, they resembled the man who, having passed through typhoid fever, rarely has it again.

In the further study of this phenomenon, Pfeiffer investigated the fate of cholera and typhoid germs when introduced into the peritoneal cavity of guinea-pigs, and found that, whereas in the untreated animal the bacteria grew rapidly and soon caused death, in the immune animal the germs became clumped together and gradually dissolved, the animal remaining in good health.

This clumping and dissolution of disease germs in the peritoneal cavity of guinea-pigs under the influence of specific immune agents is known as Pfeiffer's phenome-

1. Pfeiffer: Ztschr. f. Hyg., xix, 75; Pfeiffer and Kolle: Ztschr. f. Hyg., xxi, 203.

non, and constitutes one of the greatest contributions to our knowledge of infectious disease, for it soon became clear that similar results could be obtained if the germs were put into the peritoneal cavity of an untreated guinea-pig, provided that blood-serum from an immune animal was introduced at the same time.

The next step was to show that the serum from the sick human being would bring about similar results with the suspected organism, and the chain linking the germ to the human disease was thereby made complete.

Incidentally, however, much more was accomplished. It was next discovered that typhoid and cholera germs would undergo in a test-tube the same clumping, and sometimes the same disintegration, as that seen in the guinea-pig when brought in contact with typhoid and cholera serum, and this fact, further elaborated by Gruber and Widal, has brought the so-called Widal test—a procedure most valuable in the diagnosis of typhoid fever and many other infectious diseases.

From a known variety of serum, therefore, we can now in many bacterial diseases determine with great exactness whether a suspected germ is the one corresponding to that serum, and, *vice versa*, given a known germ, we can determine from the blood-serum whether a sick man or animal is suffering from an infection due to that germ.

The importance of these discoveries can hardly be overestimated. For example, a patient is found to have a fever with symptoms referable to the intestinal tract. An organism is isolated from the stools and shows with a known cholera-serum a specific reaction. From this knowledge it becomes certain that the patient is suffering from cholera; he is properly isolated, and possible danger to those in his surroundings is removed. Similar procedures are possible, furthermore, with typhoid and dysentery. It is impossible to say how many lives are saved annually and how much disease and suffering are prevented through these methods of diagnosis alone, made possible by the discovery of Pfeiffer's phenomenon.

This work of Pfeiffer, moreover, was of equal if not greater importance in another direction. As stated above, Pfeiffer found that by inoculating animals with gradually increasing doses of disease germs the animals could be made immune against these specific diseases. Furthermore, it became plain that the blood-serum of an

animal which had been made immune to a certain infection would give protection when introduced into the body of a normal animal. This fact stimulated investigation all over the world and, as a result, we now have not only means for preventing the occurrence of disease but also for its cure when once acquired.

For the prevention of the three diseases under discussion the method commonly employed is that of protective inoculation, which, as above stated, is a direct outgrowth of experimental work on artificial immunity in animals. Subcutaneous injections are made of dead bacteria in varying amounts, from which injections there results, at most, a mild and transient illness.

The human body, however, having overcome the infection in mild form, is for considerable periods of time thereafter in a condition to resist with unusual strength any subsequent exposure to the disease.

In cholera, for instance, Haffkine² found that the incidence of the disease among those inoculated was one-tenth that among the uninoculated.

As to bacillary dysentery, Shiga³ inoculated in Japan 10,000 people with a mixture of dead bacilli and specific dysentery serum. The incidence of the disease was, to be sure, not much affected, but the death-rate was reduced from 25 per cent. to practically nothing.

In typhoid fever, protective inoculation has been practiced to a considerable extent, especially in the British army. Leishman⁴ states that of 5,473 soldiers who were inoculated only 21 became subsequently infected, and of these but 2 died. Of 6,610 soldiers uninoculated but in the same regiment, 187 had typhoid fever and 26 died.

During the Spanish-American war, out of 107,973 enlisted men 20,738 had typhoid fever and 1,580 died of the disease. According to the English experience, protective inoculation in typhoid fever, impossible except through knowledge gained by animal experimentation, would have saved thousands of American soldiers from sickness and hundreds from death, to say nothing of the secondary typhoid fever spread by these soldiers throughout the country during their convalescence, for, as is now known, about 4 per cent. of persons who have typhoid fever become chronic carriers of the disease, through the presence of typhoid bacilli either in the stools or urines,

2. Haffkine: Bull. de l'Inst. Pasteur, Sept. 15 and 30, 1909.

3. Shiga: Osler's Modern Medicine, 1907, II, 800.

4. Leishman: Jour. Roy. Army Med. Corps, February, 1909.

or both. Similar conditions obtain in cholera and dysentery.

The rôle of carriers in the spread of these infections is a most important one, and one unsuspected until within recent years. The knowledge that such individuals may exist in any community will strengthen to a very great extent the hands of the health officer in checking the ravages of these diseases, but this source of infection could never have been discovered had not the lives of many animals been sacrificed in establishing the identity of the specific organism.

Protective inoculation for typhoid fever has been introduced recently into the United States army. I have instituted this practice⁵ at the Massachusetts General Hospital among the nurses and ward tenders, who, during the summer and fall seasons, are especially exposed to this disease.

Stimulated by the success attained through the use of antitoxin in diphtheria, much experimentation has been done in an effort to secure similar protective serums for cholera, dysentery and typhoid.

With cholera, the results thus far have not been very encouraging. In dysentery, however, favorable reports of serum treatment of those afflicted with the disease come from Russia, France, England, Austria and Japan. Shiga, for instance, treated 298 dysentery patients with a death-rate of from 9 to 12 per cent. In 212 patients treated with drugs the mortality was 22 to 26 per cent. In typhoid fever, Chantemesse⁶ treated 1,000 cases with a death-rate of 4.3 per cent. Of 5,621 patients to whom routine treatment was given during the same period, 17 per cent. died.

As the result, therefore, of the combined studies of research workers throughout the world during the past thirty years, we know what causes cholera, dysentery and typhoid; we know how the diseases are transmitted; we know how to determine whether or not an individual has one of these diseases; we know how to protect a human being against these diseases; and, finally, how to help him intelligently when he is sick.

To gain this knowledge, experimentation on many thousands of animals has been necessary. Can there be any doubt that this experimentation has justified itself?

145 State House.

5. Richardson, M. W.: Am. Jour. Pub. Hyg., August, 1909.

6. Chantemesse: Hygiène générale et appliquée, 1907, p. 577.



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The Fruits of Medical Research With the Aid of Anesthesia and Asepticism

CHARLES W. ELIOT, LL.D., M.D. (Hon.)
President Emeritus of Harvard University

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THE FRUITS OF MEDICAL RESEARCH WITH THE AID OF ANESTHESIA AND ASEPTICISM *

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BOSTON

The first public demonstration of surgical anesthesia, which took place in this hospital on Oct. 16, 1846, was the great event that we celebrate anew to-day. From this building the blessed are spread rapidly over the civilized world, the most beneficent gift which chemical and medical science has conferred on mankind. "The Death of Pain," of which Dr. Weir Mitchell sang on the fiftieth anniversary of this memorable event, has not, however, been the only precious fruit of that successful use of anesthesia in surgery. Dr. Mitchell pointed out that the anesthesia which was here demonstrated was no comet thought, which shone for a time, but gave no constant light. On the contrary, the discovery was not only to revolutionize surgery and obstetrics, but also to yield unimagined beneficial results, because it would steadily enlarge the range of medical research, and particularly would open to humane and far-seeing investigators the great field of animal experimentation.

"The radiant morning broke, and ambler hope
To art and science gave illumined scope."

Seventeen years after the discovery we here commemorate came the wonderful invention of the antiseptic treatment of wounds, whether the results of accident or of surgical interference. These two discoveries together enable the surgeon and the medical investigator to count, first, on painless operations and, secondly, on safe recoveries. In animal experimentation both the painless

* Address delivered at the Massachusetts General Hospital on the sixty-third anniversary of Ether Day, Oct. 16, 1909.

operation and the safe recovery are usually necessary to any instructive results. Together they have made the extraordinary development of modern surgery possible, and they have opened a great field of animal experimentation, which has already yielded invaluable additions to our knowledge of physiology, pharmacology and pathology. Animal experimentation has already given mankind by far the larger part of all the exact knowledge of medicine now possessed, since medical and surgical experimentation on human beings has ordinarily been impossible, at least until animal experimentation has shown the profitable direction and safe limits of experiment.

Three doubts are often suggested concerning the value of the animal experimentation, which, with the help of anesthesia and asepticism, has been earnestly prosecuted by many disinterested and humane seekers for truth during the past forty years. The first doubt relates to the connection between medical research and medical practice. Is there, as a matter of fact, any close connection between medical and surgical research and the treatment of diseases or wounds? Or, in other words, has biologic research really contributed to the success of the medical art? The second doubt is more complex and obscure, but not less crippling. What is the use of trying to ascertain the nature of a disease in animals when it is not known that the same disease occurs in men, or that the treatment successful for an animal would be successful for men? Or, in other words, is the search for truth through experiments on animals justifiable, when it is not known that the scientific results, though true, or sound as knowledge, can have any effect whatever on human well-being? The third doubt is felt most commonly by persons who make pets of domestic animals, and particularly of dogs. It may be fairly stated in this form—is truth-seeking in biology commendable, even with the help of anesthesia and asepticism, if the search be conducted at the expense of the comfort, joy, or life of animals? In the minds of many intelligent persons these questions are at a stage of doubt or inquiry; but by many others, whose temperaments and mental habits are more impetuous, these questions have already been hotly answered in the negative.

The first doubt may be resolved in two ways: first, by mention of the actual achievements in medicine which have unquestionably resulted from the last century's

studies in comparative medicine and from fifty years of active animal experimentation; and, second, by describing the legitimate hopes for the future of medicine and surgery which are founded on the rapid progress of medical science and art since bacteriology became a recognized science.

The first immense practical result of the combined study of diseases in animals and man was vaccination, instead of inoculation, as a protection against smallpox. It is not too much to say that the most destructive and appalling scourge of mankind¹ has been brought under control by Jenner's discovery "that the cowpox protects the human constitution from infection of the smallpox," the source of the infection for cowpox being "a peculiar morbid matter arising in the horse." Aristotle, Galen, Leonardo da Vinci, and Harvey studied animals and experimented on them in making their great contributions to anatomy and physiology; but their discoveries, though fundamental, did not have such immediate and world-wide applications to medical art as Jenner's discovery had. Moreover, to maintain vaccination as a universal practice among civilized nations requires the constant use of heifers to supply an uncontaminated vaccine.

Another great gain in medical art, and consequent great gain for the human race, is the newly acquired power to control infectious diseases which has resulted from the discovery of their living contagia and of the means of defeating those contagia. Under this head

1. Careful records give documentary evidence that "In the twenty-eight years before vaccination in Sweden there died each year from smallpox out of each 1,000,000 of population, 2,050 persons; during the forty years following vaccination, out of each 1,000,000 of population the smallpox deaths annually averaged 158. Such figures might be multiplied by reference to the records of other countries. . . . The decline in death rate has been limited entirely to persons below the age of fifteen. The percentage of mortality borne by children the subject of measles, scarlet fever, and whooping cough, does not differ materially from what it was a century ago." J. F. Schamberg, THE JOURNAL A. M. A., 1909, iii, 69.

The mean number of deaths from smallpox per 1,000,000 inhabitants for twenty years (1880-1899) was: in the German Empire, with compulsory vaccination and revaccination, 1.8; in Belgium and Spain, without compulsory vaccination, respectively 206 and 605. In the Prussian army there has not been a single death from smallpox since the vaccination law was first enforced in 1874.—S. W. Abbott, Buck's Handbook of the Medical Sciences, 1904, viii, 126, 130.

In seven provinces of the Philippine Islands there has been for a number of years an annual mortality from smallpox of more than 6,000—indicating about 25,000 cases. In the twelve months following the completion of vaccination in the seven provinces there was not reported one death from the disease.—Annual Report of the Bureau of Health for the Philippine Islands, 1907, p. 20.

comes serum therapy, which is now applied with extraordinary success in diphtheria,² tetanus, and meningitis. These three diseases might fairly be said to have been uncontrollable by medical art, until comparative medicine and animal experimentation discovered and brought into use their appropriate treatments. The mortality from these diseases was frightful, and the terror and suffering they caused were therefore extreme.

Many other formidable diseases have been brought under much better control through the results of medical research, such as dysentery, cholera, typhoid fever, puerperal fever,³ the plague, tuberculosis, syphilis, and certain tropical diseases caused by parasites. Sanitary science, including the diagnosis and control of contagious diseases and the detection of injurious foods and adulterated drugs, is deeply indebted to the new biologic science of bacteriology, the whole of which has been built up by researches on and with lower forms of life in connection with the higher. In thus obtaining through animal experimentation a better knowledge of the causes and sources of disease in both men and animals, the economic results have had very great importance in addition to the deliverance of the human race from suffering and untimely death. Thus, the discoveries that Texas fever was induced in cattle by the bite of a tick, that chills and fever were produced in human beings by cer-

2. In the year 1883 (the year before the bacillus of diphtheria was discovered) in the eighteen greatest cities of the world, 97 in each 100,000 of the population died of diphtheria; in 1893, 81. In 1894 (just before the general introduction of sero-therapy) 79 died, and in 1904 only 20. In twenty years, therefore the mortality had been reduced to less than one-fourth of what it had been. In New York City alone the reduction in mortality means a difference of 3,000 lives annually.—W. H. Park, Department of Health, New York City, in a pamphlet on Diphtheria.

In 1888, before the discovery of sero-therapy, there were 1,729 deaths from diphtheria in Paris; in 1895 the practice of sero-therapy became general in Paris, and the number of deaths was 435. By 1902 the best methods of using the serum was learned and definitely established; the mortality for the three years 1903-05 was 288.—Richet: Pros and Cons of Vivisection, p. 123.

3. Frequently in maternity hospitals outbreaks of puerperal fever occurred that had appalling mortality. In Vienna, from October, 1841, to May, 1843, 5,139 women were delivered and 829 died. In Paris during April and May, 1856, 64 to 347 patients died; in 1864 there were 310 deaths in 1,350 cases; in 1866, 28 deaths in 103 cases. "Women of the lower classes looked on the Maternité as the vestibule of death." In 1877-78 came the use of carbolic acid and mercury perchlorid. The death rate in maternity hospitals to-day is about 0.02 per cent.—Paget: Experiments on Animals, pp. 80, 83. Richet: Pros and Cons of Vivisection, p. 45.

tain parasites in the blood corpuscles introduced through mosquitoes, and that the contagion of yellow fever was carried from one human being to another through the body of another kind of mosquito, are all triumphs of comparative medicine and animal experimentation whose economic value is very high. The men who did this work had spent their lives in laboratories, and all their conceptions in research were based on animal experimentation.

It should also be observed that the successful treatment of diseases in man which can be controlled through the use of antitoxins depends as yet on testing those antitoxins on animals, after they have been prepared from the blood of animals inoculated with them. For example, there is no way at present of determining that a given sample of diphtheria antitoxin made from the blood of a horse is strong enough to use on a human child except by trying it on a guinea-pig or some such animal. The day may come when men will be able to prepare synthetically the effective agent of diphtheria antitoxin in a pure and isolated form; but at present biologic chemistry is utterly unable to say what that effective agent is, or what proportion of it exists in a given sample of serum. Medicine is making successful use of a complex preparation which it can neither analyze nor compound synthetically. On the whole, is it not clear that the comparative exemption of the human race to-day from the occasional pestilences and the ordinary contagious diseases, which used to agonize and devour it, is due to the fact that biologic research has placed at the service of every surgeon and physician effective means, first, of preventing disease and, secondly, of curing it? In other words, the human race received during the nineteenth century immense benefits, hardly yet understood and appreciated, from the contributions of biologic research to the medical art.

So much for actual achievements. A few words now on the legitimate hopes for the future which these achievements inspire. The prospects are brilliant, indeed. In the first place, we have already learned much about the means of overcoming the peculiar difficulties of biologic experimentation. That sort of experimentation is in general slower than experimentation in the exact sciences which do not deal with living bodies and vital processes. A single biologic experiment may need to run through generations of living and breeding ani-

mals. With prolific animals, whose generations are short, the element of time may not be exorbitant, but with the slow-breeding the time for the complete performance of a satisfactory series of experiments may be long in proportion to the thinking life of the experimenter. Thus Jenner's demonstration of the value of vaccination took many years⁴ of his observing life, and Pasteur's series of connected experiments covered his observing, imagining, and reflecting lifetime.⁵ In the next place, biologic experimentation is more difficult than experimentation in chemistry, physics, or mechanics, because of the obscurity and complexity of vital processes, and because exact weighing and measuring, which are the ordinary methods of exact inquiry, are not always possible where the subjects of experimentation are living bodies in health or in disease. In spite of these formidable obstacles, an extraordinary increase of knowledge applicable to the medical art has actually taken place since surgical anesthesia was demonstrated in this hospital, and many men have learned how to overcome in part the peculiar obstacles which beset the path of the biologic inquirer.

A second reason for expecting more rapid progress hereafter than was possible in the third quarter of the nineteenth century—productive as that period was—may be discerned in the fact that in recent years the medical inquirer has been supplied through the progress of physical science with new instruments of precision for observing and recording his facts. Thus the telephone, the *x*-rays, and all the electrical apparatus for recording fluent observations and making note of very

4. In conversation with John Hunter in 1770 Jenner suggested the prophylactic power of cowpox. A dread of disappointment led him to spend many years in observation and investigation before promulgating his discovery. He performed his first public inoculation with vaccine on May 14, 1796. And in 1798 appeared his first publication, *An Inquiry into the Cause and Effects of Variolæ Vaccinæ*, detailing his views and giving his proofs.

5. In 1853 occurred Pasteur's crucial observation that *Penicillium glaucum* destroyed the dextro-tartaric, not the laevo-tartaric acid, which indicated the relation between fermentation and living organisms. His papers on lactic acid in 1857 inspired Lister. In 1860 he began his studies of spontaneous generation, and by disproving its existence supported his experiments on fermentation. The years from 1865 to 1884 were spent in practical application of his previous work; silkworm disease (1865), studies on beer (1871), the determination of the constancy of species, the ammoniacal fermentation of urine and its check by boracic acid (1873), anthrax (1877), furunculosis, and his hospital investigations of puerperal fever (1878), chicken cholera (1880), rabies (1884).

minute portions of time and space have been valuable additions to the resources of the medical investigator.

Again, in advancing into new fields and winning their great successes biologists have clearly seen that they were only working on the edges or outskirts of a great field of beneficent discovery. Every achievement has justified a great new hope. Every success in the past justifies a strong expectation of triumphs to come. We have seen how prodigious have been the successes of medical research of the past fifty years. The legitimate hopes for the future based on these successes justify us in looking forward with delight to the continuation and enlargement of medical research, and to an endless series of its invaluable contributions to medical practice and public medicine. Now, well-grounded hope is a powerful and legitimate motive in guiding human conduct. Indeed, there is none more so, except love.

The second doubt, whether biologic research through experiments on animals is justifiable when it is not sure that the results obtained, though true, will have any immediate application to human uses in medical and surgical practice, is best allayed or removed by considering how impossible it is to tell beforehand what the ultimate results of a scientific discovery are to be. A discovery which to-day seems to be what is called "pure," that is, without application, turns out to-morrow to have applications of incalculable value. This is quite as true in biologic science as in physical. Galvani was a comparative anatomist who studied osteology, and made excellent observations on the kidneys and ears of birds. His observation that the dissected legs of frogs twitched when brought in contact under certain empirical conditions with dissimilar metals turned out to have corollaries and applications which neither Galvani nor any man of his generation could possibly have imagined. The invention of the compound microscope and the introduction of the oil immersion lens, which increased illumination and diminished spherical and chromatic aberration, made it possible to discover the infective agents which cause disease, and to study the minute changes they produce in living tissues. But these improvements in the microscope have been due to investigation of the way in which light is refracted when passed through media of different density; that is, they were obtained through physical researches not in the

slightest degree prompted or guided by any concern for human suffering, or any hope or expectation of contributing to the better treatment of disease in men or animals. Again, the ophthalmoscope, called by Helmholtz his "optical toy," was another application of inventions in physics which has had great value not only in studying and treating diseases of the eye, but also in discovering abnormal conditions of the brain.

Again, in modern medical and surgical practice the *x*-rays proved of great value for detecting bone fractures or displacements, calculi, pulmonary tuberculosis, aneurisms, foreign bodies, and many other pathologic states, for investigating the functions of internal organs like the stomach and intestines, and for curing superficial cancer. Now the *x*-rays were discovered in the course of a research on electrical discharge through attenuated gases, with no idea in the mind of the discoverer of any resulting values in medicine. Again, the researches on oxidation and combustion and the proofs of the conservation of energy were at first interests of chemists and physicists alone. The application of these conceptions to food values, to respiration and animal heat, and the demonstrations that animal bodies obey these physical and chemical laws, are seen to-day to be essential to any rational conception of bodily activities in both health and disease. And yet Lavoisier, who first stated the true theory of oxidation and combustion, never could have had the smallest vision of the innumerable biologic applications of his doctrine concerning oxygen.

Let me draw a further illustration from discoveries which are peculiarly interesting in connection with the anniversary we are celebrating. The discovery of ethyl ether by Valerius Cordius in 1540, and the discovery of chloroform by Soubeiran in 1831 and by Liebig in 1832, were both made without the slightest idea of the blessings these liquids were to confer on mankind through their use as anesthetics. The aniline dyes were elaborately studied with an eye single to their industrial uses; and their invaluable uses in bacteriology have been an unexpected and unplanned beneficial application. The basic aniline dyes have a specific affinity for bacteria, and thus they render these minute organisms easily visible. Certain bacteria are differentiated from other bacteria by peculiar staining reactions to these aniline dyes, a use never thought of or imagined

in the original chemical investigations. The modern science of pharmacology has been largely dependent on advances in organic chemistry. These advances permitted syntheses of related compounds, and the pharmacologist then studied the physical actions of these isolated compounds in the hope of securing better control of vital processes within the body. Thus through the application of methods developed in organic chemistry new local anesthetics, such as cocaine and eucain, new soporifics like sulphonal, trional, and tetroonal, new drugs for reducing fever—antipyrin, phenacetin, acetanilid—and other substances of large medical and surgical utility have been made available; but the organic chemists who made these inventions or discoveries were in search of pure scientific truth, without any thought of, or interest in, the applications of that truth.

The development of Louis Pasteur's ideas and of the applications of his ideas illustrate forcibly the way in which researches apparently in pure science, and of prime interest only to individual investigators, may yield practical results of highest value to all mankind. Starting as a chemist, Pasteur was struck by the fact that a certain mold fungus, *Penicillium glaucum*, destroyed dextro-tartaric-acid, and did not affect laevo-tartaric-acid in the same solution. From that observation he went on through studies on lactic acid formation, disease of beer, silkworm disease, anthrax, boils, puerperal fever, chicken cholera, and rabies, till he and others, stimulated by his researches, were led, step by step, to a demonstration of the microbic nature of infectious diseases, to the discovery of methods of conferring immunity to certain diseases, and to the bases of aseptic surgery. Although the ingestion of foreign bodies by living cells had been suggested as a means of overcoming invading organisms, Metchnikoff, a zoologist, first observed this phenomenon, phagocytosis, in a small crustacean, *Daphnia*. This observation was fundamental in comprehending the relation of phagocytosis to immunity, and in treating disease by stimulation of phagocytosis. One of the most striking conquests of disease in recent times is the practical abolition of yellow fever⁶ in civil-

6. According to available records 100,000 deaths from yellow fever have occurred in the United States since 1793. The cities which suffered most have been New Orleans (40,000) and Philadelphia (10,000). As late as 1878, the mortality from yellow fever in the city of Memphis, Tenn., was more than 5,000 in a

ized countries, made possible by the researches of Walter Reed and his comrades in Cuba. The happy results of their work could not have been obtained if it had not been for the previous researches of entomologists who were interested in the scales and veins on the wings, and the scales and hairs on the bodies of mosquitoes. The pure entomologists had used these phenomena as means of classifying mosquitoes, and had then studied the breeding habits of the different varieties of mosquitoes. The same remark might be made concerning the entomologic researches into the habits of the tick, which is capable of infecting cattle with Texas fever.

These are only a few of the more striking examples of the way in which facts obtained in a disinterested search for truth, whether in biology, physics, or chemistry, have subsequently proved to be of the highest importance in medical and surgical practice, and in sanitary science. There are innumerable instances in the history of science and art in which discoveries made without any reference whatever to applications for the benefit of mankind have turned out to be sources of immense benefits. Hence, the lack of certainty as to the results of a given biologic research establishes no presumption whatever that the research should not be made, or that it is not justifiable. In this respect there is no distinction between the bio-

single epidemic. About 25,000 are recorded for Rio de Janeiro and nearly 36,000 for the city of Havana from the same cause.—James Carroll in Osler's *Modern Medicine*, ii, 739.

YELLOW FEVER DEATH RATE IN HAVANA, 1870-1906, PER 100,000 POPULATION:

Report of the National Sanitary Department of the Republic of Cuba, 1906, p. 79.

Before American intervention.	After American intervention.
1870 300.5	1898 67.8
1880 324.5	1899 42.5
1890 153.6	1900 124.0
1895 275.8	1901 6.9
1896 639.5	1902 0
1897 428	1903 0
	1904 0
	1905 8.0
	1906 4.3

The mortality during the month of October, between the years 1889 and 1899, ranged from 240 in 1896 to 25 in 1899 (average for ten years 66.27). After Reed's work in 1900, Gorgas began his campaign, and in November, 1901, reported, "During the month we have had no cases and no deaths from yellow fever. Last year (1900) we had during this month 214 cases and 54 deaths. This year the last case occurred September 28, that is, we have gone over two months without a single case or death belonging to Havana." This record has been continued, and Havana has ceased to be one of the epidemic foci of the disease.—G. M. Sternberg: *Buck's Handbook of the Medical Sciences*, viii, 585.

logic sciences and the so-called exact sciences of chemistry and physics; and within biologic science itself no distinction should be made between a research into the nature or source of a disease or morbid condition, and a direct search for a cure or a promising treatment. Hence well-directed animal experimentation is clearly not only justifiable, but altogether expedient and desirable, even when it is not sure that the results obtained will have any immediate application to medical and surgical practice.

The third doubt which I propose to examine is this: Is truth-seeking in biology commendable, even with the help of anesthesia and asepticism, when the research must be conducted at the expense of the comfort, joy, or life of animals? This doubt starts the whole question about the proper relation of mankind to the other animals which live with man on the surface of the earth and in its atmosphere. The traditional idea on this subject has been that mankind has dominion "over every living thing that moveth upon the earth," and may use every living thing as he pleases for his own advantage. Accordingly, men train many sorts of animals to labor for them and serve them. The subjection of many animals to human uses is considered, indeed, one of the evidences of civilization. Both civilized and savage men kill animals in order to eat them. Millions of creatures are killed daily for human food.⁷ People have no scruple whatever about destroying animal life for human uses. The habits and the natural joys of animals are interfered with on an immense scale by the most humane people without the slightest compunction. Think what it means to millions of cows every year that their calves are killed and they are kept for the most part tied up in barns. Think what indifference to the potentialities of animal life and joy the immense trade in eggs implies. How absolutely insignificant is the number of animals used for animal experimentation in all the scientific laboratories compared with the daily use of animal products the world over as food and clothing for mankind! Immeasurably more good is likely to come to mankind

7. Every year there are slaughtered in the United States more than 50,000,000 beefs, sheep, and hogs, and 250,000,000 chickens, turkeys, ducks, and geese. Last year more than 360,000 dogs and cats were killed in a single year in twenty of the largest cities of the country, merely to remove stray animals from the streets. In New York City alone during the past fourteen years more than 800,000 cats and 400,000 dogs have thus been destroyed.

from the few hundreds of animals used in medical and surgical research than from a hundredfold their number used as food or clothing. Is the old conception that the animal as well as the vegetable kingdom is for the use of man a wrong one, or is special regard to be paid to those few animals which are made the subjects of medical and surgical experiment?

Man not only makes use of all sorts of animals for his own advantage, but he destroys without the slightest compunction multitudes of creatures that he considers noxious to him. The careful housewife kills as many flies, spiders, and vermin as possible. A city threatened with bubonic plague hastily destroys all the rats within its borders. No community has the least compunction about exterminating any insect injurious to vegetation, if it can. It cannot be seriously questioned that this has been and still is a rational state of mind in the human race. If the educated public could see clearly the immense benefits to mankind which have already come and may reasonably be expected to come in much larger amount from the experiments on animals which are necessary to the progress of medical research, if the public could only realize the saving of human suffering and woe which has already resulted and is sure to result in still greater proportion from the sacrifice of a very limited amount of animal comfort and joy, the world would hear nothing more of objections to medical research. The most tender-hearted human being is ordinarily unable to fix a limit to the number of inferior animals he would sacrifice to save the life of one human baby. Now a baby is itself only a hope or a potentiality, its present power of enjoyment being extremely limited. "How much, then, is a man better than a sheep?" (Matthew xii, 12). What mother could fix a limit to the number of times a comfortable horse should be bled moderately, or to the number of guinea-pigs that should be sacrificed, in order to save her baby attacked by diphtheria? The tender-hearted men and women who object to animal experimentation have no vision of the relief of human beings from agony and woe which has come out of animal experimentation. If they had any such vision, they would themselves manifest extraordinary cruelty and inhumanity in opposing medical research; in their present blindness they attribute delight in inflicting suffering to the patient, far-seeing, and far-hoping seekers for biologic truth. Which is the truly

humane and merciful man, the director of the Rockefeller Institute for Medical Research, who by producing cerebrospinal meningitis in a few monkeys⁸ lately succeeded in providing men with a successful mode of treating that formidable disease, or the lawyer or newspaper writer who endeavored to prevent those experiments on monkeys, and is ready to let the human race remain helpless on the occasional visitations of that heretofore fatal disease? Humanity and mercy are conspicuously the attributes of medical research in the eyes of all people who can see what it has already done and what it promises to do.

The civilized world has come to believe in freedom of inquiry in all fields as the best means of progress in knowledge, in manners, and in righteous living. Now the field of inquiry from which, within the last sixty years, mankind has received the largest visible, tangible, concrete, demonstrable benefits is the field of medical research, applied in the medical and surgical art, and in sanitary science. If freedom of inquiry be in general expedient and righteous, should not inquiry be free in this most productive of all fields? To secure and maintain this freedom against the assaults of ignorance and misdirected sentimentality it is only necessary that the public should know what medical research has done and is likely to do.

The appropriateness to the day we celebrate of the subject of this address will not be doubted by anyone who bears in mind the fact that anesthesia and asepticism have been indispensable to the medical research of the last forty years.

8. Dr. Flexner used about 25 monkeys and perhaps 100 guinea-pigs. He now has records of nearly 1,000 human beings treated by the serum, with a continuation of the first successes—a reversal of the percentages, from 70-80 per cent mortality to 70-80 per cent recovery, and already a saving therefore of approximately 500 lives. Dr. Flexner describes the experiences of the monkeys in the experiments; most of them became profoundly and stuporously intoxicated by the disease, and therefore did not suffer pain.



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OCT 4 1910

Animal Experimentation in Relation to Our Knowledge of Secretions, Especially Internal Secretions

**S. J. MELTZER, M.D., LL.D.
NEW YORK**

DEFENSE OF RESEARCH PAMPHLET X

**Issued by the Council on Defense of Medical Research
of the American Medical Association**

**"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.**

**CHICAGO
AMERICAN MEDICAL ASSOCIATION
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ANIMAL EXPERIMENTATION IN RELATION TO OUR KNOWLEDGE OF SECRETIONS, ESPECIALLY INTERNAL SECRE- TIONS

S. J. MELTZER, M.D., LL.D.
NEW YORK

INTRODUCTORY REMARKS

Progress in pure science and in industry brings essentially luxurious delights to mind and body; the object of advance in the science of medicine, however, is in the first place to procure indispensable necessities for life and health. Necessities certainly come before luxuries. Ought we not expect to find sane humanity devoting its energies above all to the furtherance of progress in the domain of medicine? Unfortunately, just the reverse seems to be true; medical science again and again has to struggle with obstacles in its forward march. These obstacles are not only those which are wilfully thrown in its path by ignorant, ill-balanced and noisy individuals of both sexes; even the noble tendencies of pure science not infrequently have been quite obstructive to a wholesome development of the science and practice of medicine. The root of the evil is that not many have a vivid conception of the immensity of the gap which existed and still exists between what medicine really ought to be and what it was and largely still is, nor a proper conception of what the small group of workers have actually accomplished in the various departments of medicine.

In the following pages I shall give an outline of the progress made in our knowledge of glandular secretions, especially of the marvelous progress made in a brief time in our knowledge of internal secretions. By this outline I intend to demonstrate the inestimable service which experiments on animals have rendered to that feature of the science of medicine. The authenticated facts in this

paper may thus be instrumental in disproving insinuations and accusations often raised against animal experimentation by two diametrically opposite camps: high science and low ignorance; the former frequently insinuating that the results are not sufficiently exact to be ranked as scientific work, and the other that animal experimentation has never been of any use either to science or to the practice of medicine.

The term "internal secretion" has been in use less than two decades, and the instructive facts which are covered by that term began to make their appearance not much longer than a quarter of a century ago. The knowledge of this form of secretion, young as it is, compares favorably with the knowledge of glandular secretion in general, which can look back on a history of nearly four centuries. The following two factors are responsible, I believe, for the marvelous progress of this new chapter of experimental medicine. In the first place, the recent investigations of the ductless glands were carried on purely by biologic methods of research. The second factor is to be found in the important fact that these investigations had the great advantage of a harmonious cooperation of critical animal experimentation, scientific clinical observations and intelligent analysis of surgical results. I lay great stress on the biologic character of the method of investigation as an important factor in the progress of medicine. To my mind even the growth of our knowledge of glandular secretion in general can be traced back essentially to the purely biologic investigations which in the course of the slow development of the medical sciences in the past few centuries were carried on spasmodically. I shall attempt to illustrate this statement by some data, but before doing it I shall try to elucidate what I mean by the term of pure biologic research.

BIOLOGIC METHOD OF RESEARCH

The marvelous growth of the natural sciences since the sixteenth century can be traced back to the scrupulous observation of the following two simple requirements of methods of observation: (1) The phenomena of nature have to be studied by actual observations, and (2) the correlations of these phenomena have to be established according to their respective merits and free from any extraneous considerations. The first requirement needs no discussion; it is evenly applicable to the

investigations of all the divisions of natural science. The second requirement, however, presents different aspects in the different domains. As far as the inorganic world is concerned, the requirement is quite simple; it is directed chiefly against the inveterate interference of metaphysical theories with the interpretation of natural phenomena, and the requirement of freedom from such interference is here self-evident. Science has to deal with the provable; and since metaphysics avowedly deals with unprovable problems, it is evident that these two domains cannot coincide. It is different, however, when dealing with the phenomena of the living world. The correlation of these phenomena can be studied in the first place as in the inorganic world, exclusively with relation to themselves, without regard for extraneous domains. This method of study of the phenomena of the living world I designate as the purely biologic method of research. The living phenomena, however, can be also studied with a view of reducing them to phenomena of the inorganic world. This line of study I would designate as the physicochemical study of biology.¹

It is evident that in the latter line of investigation of living phenomena the rational requirement of freedom from extraneous considerations suffers a serious setback.²

The history of medical science shows that there was, consciously or unconsciously, a continual struggle between the followers of the two methods of investigation, sometimes the one, sometimes the other gaining the supremacy. This is not the place to enter on the

1. The physicochemical study of biology should not be confounded with the employment of physicochemical methods in biologic research. All researches of function are necessarily carried on by physical or chemical methods. For instance, the removal of an organ is a physical, and the injection of an extract of this organ is a chemical method; at the same time the object of such investigations is of a purely biological character; it tries to establish the importance of that organ for the life of the animal. But the attempt to ascribe the function of an organ to some well defined chemical constituent of that organ, for instance, to ascribe the normal action of the thyroid gland to its iodine content, belongs to the chemical studies of that organ. It is a fact that even distinguished physiological writers are not infrequently guilty of confounding the employment of physicochemical methods in the study of biology with the physicochemical studies of biology.

2. In these attempts to reduce the living phenomena simply to those of physics and chemistry even traces of metaphysical dictates can sometimes be detected, if we keep in mind that the interference of materialistic metaphysics is not much less deleterious to wholesome studies of natural sciences, than the interference of spiritualistic metaphysics.

history of this struggle; nor shall I attempt to dwell here on the merits of each side. There can be no doubt that both methods are absolutely legitimate, in fact, indispensable, and ought to supplement each other. I wish, however, to record here my opinion that, as a matter of fact, medical science in all its aspects has profited so far vastly more from the purely biologic researches than from the physicochemical researches in biology. This statement certainly holds good with reference to our knowledge of internal secretions; but, as stated above, it is true also, at least to a large degree, for glandular secretion in general.

GLANDULAR SECRETION

Previous to the new era in anatomy all small semi-solid brown structures in the body were designated as glands. The filtration of the blood was the function assigned to these little lumps of tissue. With the regeneration of anatomy by Vesalius and other anatomists of the sixteenth century the distinction was made for the first time between secreting and blood glands. The physiology of secretion, however, did not benefit very much from the great progress made in anatomy. In the sixteenth century even the brain was considered as a secreting organ: it picked out the vital spirits from the blood and secreted mucus through the lamina cribosa into the pharynx. Studies on the dead body alone, the chief object of study in the sixteenth century, could not reveal the real action of the living gland. It was not until the middle of the seventeenth century that the knowledge of glandular secretion began to assume a rational scientific aspect. Many writers trace this knowledge back to Malpighi's work on the liver, which was published in 1665. It is, however, a fact that important communications were made on the secreting glands previous to the appearance of Malpighi's work. It was the marvelous discovery of the circulation by Harvey, proclaimed to the world in 1628, which started the physiologic studies on the glands. Harvey discovered the circulation by studying it in living animals. This gave a great stimulus to the employment of animal experimentation in the study of the phenomena of life, and for many decades there was a rich harvest of discoveries of important facts

in physiology.³ By experiments on animals Johann Georg Wirsung (or Moritz Hoffmann) discovered in 1642 the duct of the pancreas, Thomas Wharton discovered (in 1652) the duct of the submaxillary gland, Nicolas Stenson discovered (in 1662) the duct of the parotid gland and also the lachrymal duct, and Rivinius (in 1679) discovered the ducts of the sublingual glands. De Graaf succeeded in 1664 in collecting pancreatic juice from the living animal, and Brunner discovered (in 1686) the glands of the duodenum, designated by his name. Malpighi (1628-1694), besides his great work on the liver, the gall-bladder, the bile ducts and on the kidneys, studied also the sweat and sebaceous glands of the skin. All these discoveries led up to the conception of (an external) secretion by glands provided with ducts. In contrast to these glands another group was designated as ductless glands, including in this group at first even the lymph glands. After the discovery by Aselli (1623) of the chyle-bearing vessels, and the discoveries by Pequet (1651), by Budbeck (1652) and by Thomas Bartholinus (1653) of the lymph vessels, receptaculum chyli and the thoracic duct, the lymph glands were separated for good from the other glands. The ductless glands comprised then the spleen, thymus, thyroids and adrenals.

Near the close of the seventeenth century the biologic researches into the nature of glands came to a standstill. Physico-chemical investigations and interpretation of living phenomena came to the front, and iatrophysicists and chemiaters held the stage for a good many years. In fact, all pure biologic researches seemed to have become silenced, at least greatly overshadowed, by the tendencies of physico-chemical investigations of biology, which gradually forged their way to the front in the course of the seventeenth century. The mathematical and physical sciences possessed a lustre given to them at that epoch by the brilliant astrophysical researches of Galileo (1564-1642) and Kepler (1571-1630). The good work of Borelli (1608-1679) on animal motion, which

3. Animal experimentation was then a much less dangerous occupation for the investigator than the study of anatomy on a human cadaver. The leaders of human destiny at that age had no hesitation in killing men and even mutilating their dead bodies for any trivial reason, but objected to the use of the dead bodies of men when medicine and science could profit by it—just as the misguided of both sexes of our own day are ready to kill and maltreat all sorts of animals for personal profit, sport or vanity, but manifest a perverse moral indignation when such animals are used for the benefit of medicine and mankind.

was based on purely mechanical principles, the mechano-biologic investigations of members of the newly organized Royal Society, for instance, the demonstration by Robert Boyle (1627-1691) of the danger of the vacuum to life, the demonstration of Robert Hooke (1635-1703) of the importance of artificial respiration, or the introduction of transfusion by Richard Lower (1631-1690)—all these factors were instrumental in demonstrating the fruitfulness of mechanical and physical analysis of living activities. The significance of chemical processes had begun to impress the minds of medical men already in the previous century by the aggressive teachings of Paracelsus (1490-1541). Under the influence of the teachings of Van Helmont (1577-1644), the discoverer of carbonic-acid gas; of Franciscus Sylvius (1604-1672), the founder of the first chemical laboratory, and of their pupils, chemical interpretation of biologic phenomena developed into a leading system.

For a very long period iatrophysicists and chemiaters struggled for supremacy in the fields of biology and medicine, pushing pure biologic research nearly entirely out of sight. During the eighteenth century practically no progress was made in the knowledge of glandular secretion. It is true that at about the middle of that century some experiments on gastric secretion were carried out on animals by Reaumur (1683-1757), by John Hunter (1728-1793), and especially by the celebrated Abbé Spallanzani (1729-1799). But these experiments dealt chiefly with the process of gastric digestion and the nature of gastric juice; they did not concern themselves with the character of the glands and the act of secretion. The first important biologic investigation of secreting glands came to light in 1830; it was the celebrated comparative anatomic study of the secreting glands in the entire animal kingdom by Johannes Müller. About a decade later the animal cell was discovered; this gave a great stimulus to pure biologic researches, but they were essentially of a morphologic nature. The studies of the functional side of life became dominated, however, even more than ever by the physicochemical conceptions of that epoch. The brilliant physicophysiologic investigations of Du Bois Reymond, Helmholtz and Ludwig and their pupils, at about the middle third of the last century, were especially instrumental in establishing the absolute reign of mechanical conceptions in the domain of physiology. It was in harmony with these

physical tendencies that secretion was looked on, as in olden times, as a mere mechanical process of filtration. A great deal of energy has been spent and brilliant experimental work done in support of this contention. Did these marvelous efforts greatly enrich our knowledge of the processes of secretion with actual facts? I believe that the attitude of Heidenhain⁴ in assuming a "vital activity" of the epithelial cells was by far more fruitful in this direction. With the assumption of a vital activity Heidenhain claimed nothing else but the right to study living phenomena with reference to themselves. He did not deny that this vital activity might be explained one day by some new physical and chemical laws. He merely found it more profitable to study at present the living phenomena as they are, preferring no physicochemical interpretation to a premature interpretation by imperfectly known inorganic laws. Thanks to these efforts of Heidenhain and his followers, considerable progress has been made in the recognition of the processes of secretion and the intracellular changes accompanying them. We have thus now recognized the fundamental fact that secretion is a specific function of the glandular cells, just as contraction is a specific function of a muscle cell. The difference between the various secretory products has its origin in the specific secretory activities of the cells belonging to the different secretory organs.

I shall, of course, not enter here on a recital of the great amount of work done in the last sixty years on glandular secretion. I believe, however, that it is perfectly safe to state, as I did above, that the important facts which we know at present with regard to glandular secretion in general were discovered chiefly by means of purely biologic investigations.

THE FUNCTION OF DUCTLESS GLANDS

Since the discovery of the ducts of the various secreting glands, the spleen, thymus, thyroid and suprarenal glands were grouped together, as stated before, under the term of ductless glands. That term is still in use in the literature, except that in this group the spleen is now replaced by the pituitary body. The glands of this group have been known for more than four centuries. What are their functions and do they have any? Schäfer⁵

4. Heidenhain: Hermann's Hanhb. d. Physiol., v, Part 1.

5. Schäfer: The Oliver-Sharpey Lecture, Brit. Med. Jour., May 30, 1908.

tells us of the satirical comments made by Montesquieu nearly two hundred years ago on various essays offered in solution of the prize question: What is the use of the suprarenal glands? "Perhaps chance may some day effect what all these careful labors have been unable to perform," says Montesquieu. More than a century later we find the brilliant physiologist, Magendie,⁶ telling his hearers:

I have nothing to say on the suprarenal capsules. Since nobody any longer believes in *atra bilis* the capsules have ceased to be its secreting organ. . . . What function does the thyroid gland have? Nobody knows it. . . . That organ surely deserves the investigation of physiologists. . . . *Does it not attain in cretins an enormous size?*⁷ while the other organs become reduced?

However, we need only go back less than three decades to find the same profession of ignorance by competent authors. In the well-known work by Herrmann published in 1883,⁸ it is stated in one line that we know nothing of the functions of the thyroids and adrenals. However, it was in the very same year that the "chance" came of which Montesquieu wrote. The precious chance came in the first place as a culmination of various activities with reference to the significance of the thyroid glands. But the light which was shed on the vital importance of these glands lit up the entire field of internal secretion which had remained impenetrably obscure for many past centuries.

THE IMPORTANCE OF THE THYROID GLANDS

In the course of the preceding centuries numerous theories were put forward regarding the significance of the thyroid glands. However, already at an early part of the last century various writers, among them especially Hofrichter,⁹ analyzed these theories and discarded them. The theory which in the second third of the last (19th) century gradually gained most favor was the one put forward in the eighteenth century by Prochaska, namely, that the thyroid as well as the adrenal glands had, like the thymus, no significance for extrauterine life. It is true that already in the fifties of the last century experiments were published indicating the great

6. Magendie: *Leçons sur le système nerveux*, 1841.

7. Italics mine. We know now that the opposite is true.

8. *Handbuch d. Physiol.*, v, 2.

9. Hofrichter: *Meckel's Arch. f. d. Physiol.*, 1820, vi, 186; *Fuhr: Arch. f. exper. Path. u. Therap.*, xxi.

importance of these glands in adult life. We shall speak of these experiments later more fully. These publications made, however, no impression on contemporary physiology. That science was dominated then, as stated before, by physicomechanical conceptions and manifested neither great interest in pure biologic researches nor special confidence in their results. There was (and still is) an ever-present tendency among the approved physiologic investigators to ascribe such results to some inadequate technic or to some carelessly overlooked secondary factor.

The first step in the new direction was made within the clinical domain, at first without apparent bearing on our question. In 1873 Sir William Gull¹⁰ reported 5 cases of middle-aged women who had a cretinoid appearance, a more or less bulky form and other symptoms which characterized these cases as presenting a separate and new type of disease. In 1878 W. Ord,¹¹ who had had similar cases under observation since the sixties, reported one case which came to autopsy. The most striking finding was the mucin-like masses in the subcutaneous tissue which caused Ord to designate the new type of disease as myxedema. Among the post-mortem findings of this case atrophy of the thyroid glands was noted. The next contribution came from the surgical domain. With the general introduction of antisepsis at the beginning of the seventies, surgeons ventured to extend their activities to regions which formerly seemed to be inaccessible to their interference. Large goiters which are prevalent in some regions, especially in Switzerland, were now treated by radical operation. In April, 1883, Kocher,¹² of Berne, gave an extensive report of the after-effects of such complete removals of goiterous glands. The patients showed a peculiar complex of symptoms which Kocher designated as cachexia strumipriva. He looked then on the symptoms as being due to some degree of asphyxia caused by this operation. A few months before Kocher's report appeared Jaques Reverdin¹³ of Geneva, made a similar but less extensive report, which, however, seems to have at first passed unnoticed. In November of that year Felix Semon¹⁴ called the attention of the Clinical Society of London to the simi-

10. Gull: Tr. Clin. Soc., 1873, vii.

11. Ord, W.: Tr. Clin. Soc., 1878, xiii.

12. Kocher: Arch. f. klin. Chir., 1883, p. 254.

13. Reverdin: Rev. méd. de la Suisse romande, 1883.

14. Semon: Tr. Clin. Soc., November, 1883.

larity of the symptoms of the postoperative cachexia with those of myxedema and suggested that in both cases the complex of symptoms might be due to an absence of the thyroids, which glands, therefore, may be of fundamental importance to the life of the human adult. This statement made such a deep impression on the society that a committee was appointed to investigate the entire subject. It should be mentioned that a few months before Reverdin,¹³ in a second communication, recognized the similarity of the two types of phenomena and designated the complex of symptoms which follows the complete removal of the goitrous thyroids as operative myxedema. This communication also escaped general notice. But it was the means of calling forth the statement of Schiff,¹⁵ who was then professor of physiology at Geneva, that in experiments made by him as early as 1856 he found that many of the animals succumbed after the complete removal of the thyroid glands. These results he communicated at first to the academy at Copenhagen and later made them known in a separate communication which appeared in 1858.¹⁶ These communications apparently made not the slightest impression on contemporary physiology. Schiff¹⁷ now repeated and extended his former experiments and found that especially in dogs the complete removal of the thyroids is mostly a fatal operation, the animals dying with symptoms quite similar to many of those observed after complete (surgical) removal of goitrous thyroids in human beings. A statement of great interest was soon made by P. Bruns.¹⁸ He discovered in the literature from the sixties a report by P. Sick¹⁹ of a case of complete removal of goitrous thyroids in a young boy.

He hunted up the operated subject and discovered that the patient, who was now at the end of the thirties, had the size and appearance of a mentally and physically backward boy—a surgical cretin. Autopsies of naturalcretins then revealed the further fact that the thyroid glands were deficient in these cases.

These various communications brought to light the following series of new facts: (1) natural absence of the thyroids in adults causes myxedema; (2) natural

15. Schiff: Rev. méd. de la Suisse romande, 1883.

16. Schiff: Untersuchung über die Zuckerbildung in der Leber, etc., Würzburg.

17. Schiff: Arch. f. exper. Path., xviii.

18. Bruns, P.: Samml. klin. Vortr. (Volkmann's), 1884, No. 244.

19. Sick: Württemb. med. Cor.-Bl., 1867, No. 25.

absence of the thyroids in children causes arrest of growth and cretinism; (3) complete removal of the normal thyroids in animals is a fatal operation; (4) complete surgical removal of the goitrous glands in children causes surgical cretinism; (5) complete removal of these glands in adults causes surgical myxedema. These facts indicated clearly enough that the thyroid glands are of fundamental importance to the health and life of man and animal. Schiff,²⁰ however, brought forward still stronger evidence in favor of this thesis. He implanted in the peritoneal cavity of an animal one of its own thyroids and found that this animal survived for a long time the removal of the second thyroid—a sure proof that the fatal result of the complete removal is caused by the absence of the function of the thyroid gland and is not due to secondary lesions caused by the operation.

In the following years numerous experimental investigations in animals confirmed the main facts. The most extensive and important of these investigations were those of Victor Horsley,²¹ then a member of the above-mentioned committee appointed by the Clinical Society, and of Ferdinand Fuhr.²² As an instructive fact we shall mention that these experimental investigations were carried on mostly by non-official physiologists. Of the official physiologists it was H. Munk²³ alone who took an active share in this work, and this with the persistent claim that the observed results were due to an irritation of the adjoining nerves during the "careless" removal of the thyroid glands. There were also a few reports of experiments in which no profound effects were observed to follow the complete removal of the thyroids. Some of these reports, however, were based, as Fuhr conclusively has shown, on erroneous observations. The submaxillary glands were removed instead of the thyroids. Other failures could be explained by the facts that either the removal was in fact not complete, some parts of the thyroid remaining behind, or that in these cases there were some accessory thyroids which had not been removed.

All these investigations had in the first place the one important practical result, that surgeons stopped the practice of complete removal of goitrous glands. This

20. Schiff : Rev. méd. de la Suisse romande, 1884.

21. Horsley : Suppl. Tr. Clin. Soc., 1888, xxi.

22. Fuhr : Arch. f. exper. Path. u. Therap., 1886, xxi, 387.

23. Munk : Sitzungsb. d. Berl. Akad. d. Wissenschaft., 1887, p. 823; 1888, p. 1059.

they could do the more readily, since the investigations brought the important fact to light that the presence of only a small part of the thyroid was sufficient to keep up its function and to obviate the ill-effects of the removal.

The complete removal of goitrous glands was followed not only by serious chronic symptoms, but also by severe acute attacks of tetany, terminating sometimes fatally. Seven such deaths were reported from the celebrated clinic of Billroth in Vienna alone.²⁴

The above-mentioned experiments of Schiff on the implantation of the thyroid in the abdominal cavity of dogs gave rise to the attempts of various surgeons to cure operative and normal myxedema by grafting pieces of human thyroid, removed at operations, into the peritoneal cavity or in the subcutaneous tissue of such patients. The most striking result of such a procedure was reported by H. Bircher²⁵ in one case. After each new implantation practically all pathologic symptoms disappeared for a long period. The success, however, was not permanent. Apparently the grafted fragments did not resume at the new place the function of the thyroid; they gradually became absorbed. The fact, however, that during the absorption of the grafted pieces the symptoms of the cachexia were kept in abeyance gave rise to the idea that the administration of an extract of the thyroid might perform a similar office. The first attempts to test this idea were made by Colzi²⁶ and by Vassale,²⁷ who injected such extracts intravenously into animals. In 1891 George Murray²⁸ established the important fact that subcutaneous injection of thyroid extract in man is capable of abolishing all the symptoms of myxedema. This was followed by the announcement of Howitz,²⁹ in July, 1892, and by Mackenzie³⁰ and

24. See Anzeige d. k. k. Gesellsch. d. Aerzte in Wien., 1883. No. 31. If the animal experiments which shed so much light on our subject had been carried out before the attempts were made by surgeons to perform the complete removal of goitrous glands in human beings, a great deal of misery and many deaths might have been spared. Experiments on various species of animals should be extensively performed before any new serious operation on human beings may be attempted. But while nobody thinks of dictating by law to the surgeon what operations he may or may not perform, there are individuals all over the world who wish to have laws enacted suppressing or crippling experimentation on animals. What a perversion of reason and morals!

25. Bircher, H.: Samml. klin. Bortr. (Volkmann's), 1889, No. 357.

26. Colzi: Sperimentale, 1884.

27. Vassale: Centralbl. f. d. med. Wissensch., 1891, p. 14.

28. Murray: Brit. Med. Jour., Oct. 10, 1891.

29. Howitz: Lancet, 1892, ii, 1213.

30. Mackenzie: Brit. Med. Jour., Oct. 29, 1892.

Fox,³¹ in October of that year, that the same result can

31. Fox: Brit. Med. Jour., Oct. 29, 1892.

be obtained by the administration of the thyroid gland, even cooked, by the mouth. The last named communications demonstrated that the effective principle of the gland is destroyed neither by heat nor by digestion. It was further evident that the action of the gland was not specific, inasmuch as the extract of glands of various species of animals acted favorably on human patients. These statements were soon generally confirmed all over the world and thyroid therapy became a well-settled fact.

We thus learn an impressive lesson. While the mere reasoning of many brilliant minds carried on for four centuries shed no light on the significance of the thyroid gland, the intense activity of modern experimental medicine managed to bring to light in less than ten years the following important facts with regard to these glands: (1) the thyroids are of fundamental importance to life and health; (2) a new disease was established: the "natural" atrophy of the thyroid in adult life leads to myxedema; (3) the real nature of a well-known disease was recognized: cretinism is infantile myxedema; (4) complete removal of goitrous thyroids during infancy leads to cretinism and their removal during adult life may bring on either myxedematous cachexia or tetany; (5) surgeons learned two important lessons: on the one hand not to perform a radical removal of the goitrous glands, and, on the other hand, that the ill-effects can be obviated by leaving behind a small part of the gland; (6) extract of the thyroid gland is capable of removing the symptoms due to the natural or artificial absence of this gland. In short, by the methods of biologic research we learned in less than ten years a great deal of the physiology, pathology and therapy of the thyroid glands.

The studies were fruitful in many other directions, which, however, can be only indicated here by a few words. By experiments on animals and by observations on human beings it was found that the unrestricted administration of thyroid extract brings on a condition which is very similar to that pathologic complex known as exophthalmic goiter or Graves' disease. This fact led up to the conception that Graves' disease consists in the normal overproduction of the thyroid function—hyperthyroidism. This conception was fruitful in developing medical and surgical therapeutic measures on which we cannot dwell here.

Furthermore, it was found that thyroid extract has a therapeutic value in diseases other than myxedema and cretinism, for instance in obesity, scleroderma and some other skin diseases.

In the course of all these investigations the important discovery was made by Baumann,³² in 1895, that the thyroid contains iodin in an organic compound which some believe to be closely connected with the main function of the gland. It was further found that the thyroid extract exerts a certain influence on the resistance of some animals to some poisons and that this influence is in proportion to the iodin content of the gland.³³

There is, however, one brilliant chapter in the investigations of the thyroid which should be told in somewhat greater detail. The above mentioned investigations on the thyroid left some unexplained points. The effects of the radical removal of the thyroids in human beings were far from being uniform; sometimes myxedematous and sometimes tetanic symptoms prevailed. In animals the effects of the removal of the thyroids were nearly exclusively of a tetanic character. Finally the most puzzling fact was the apparent harmlessness of the removal of the thyroids in some species of animals, as, for instance, in rabbits. At first the idea suggested itself that with regard to the importance of the thyroid there was a difference between carnivorous and herbivorous animals. Further animal experimentation, however, threw a flood of new light on these puzzling problems.

THE PARATHYROID GLANDS OR THE EPITHELIAL BODIES

Sandstroem³⁴ discovered in 1880 small definite bodies consisting of cell masses in proximity to the thyroids. He gave them the name of parathyroid glandules. Sandstroem assumed that these cell masses represent undifferentiated embryonal thyroid tissue. Very little attention was paid to these bodies until 1892, when Gley³⁵ conceived the hypothesis that these bodies play an important rôle in the phenomena following the removal of the thyroids. On the basis of this hypothesis he discovered the important fact that after the removal in rabbits of the two free parathyroids, in addition to the removal of the thyroid glands, well-defined tetanic manifestations occur also in these animals. Removal of the

32. Baumann : Ztschr. f. physiol. Chem., xxi, 319.

33. Hunt, Reid : Studies on Thyroid, Bull. No. 47 Hyg. Lab.

34. Sandstroem : Jahresb. f. Anat. u. Physiol. (Hoffmann and Schwalbe's), 1881.

35. Gley : Arch. de physiol. norm. et path., 1892.

thyroid glands alone or of the two parathyroids alone is not followed by any untoward symptoms. The communications of Gley were instrumental in bringing out a large number of researches dealing with the significance of the parathyroids, of which we shall mention here only two. A. Kohn³⁶ brought out by careful histologic investigations that there are most frequently four parathyroids, two of which are frequently imbedded in the tissue of the thyroid glands. The removal of the thyroids, therefore, also removes two of the parathyroids, and the removal of the thyroids and parathyroids in Gley's experiments meant complete removal of all the parathyroids. Kohn established further that the parathyroids do not represent an embryonic stage of the thyroid tissue, but are independent bodies composed of epithelial cells, and he suggested the name of epithelial bodies for the parathyroids. The second series of important researches were those of Vassale and Generali,³⁷ who reported a long series of experiments in which they succeeded in removing in animals either the thyroid tissue alone or the parathyroids alone, and arrived at the conclusion that the removal of the thyroids alone leads to myxedematous symptoms, and the removal of the epithelial bodies alone leads to tetanic symptoms. It cannot be claimed that this problem is even now completely solved. But the mass of evidence at hand is overwhelmingly in favor of the view, that the epithelial bodies are independent organs, the removal of which favors the onset of tetanic manifestations, and there can hardly be any doubt that the tetanic symptoms following in some cases the radical removal of the thyroids are due to the simultaneous removal of all the parathyroids or the profound interference with their vascular supply. The variability of the anatomic relations of these bodies with the thyroid glands explains the variations in the surgical and experimental results. As to the functional relations of these two organs to one another, some believe that they are entirely independent of one another; others again assume that there is a definite interdependence between thyroids and parathyroids; but as to the nature of interdependence some believe with Gley that it is supplementary; others that it is antagonistic in character. The subject is not yet settled and we need not dwell on it.

36. Kohn, A.: Arch. f. mikroskop. Anat., Bd. 44, 1894.

37. Vassale and Generali: Arch. ital. de biol., xxv, xxvi.

This new theoretical knowledge brought about by animal experimentation is commencing to bear important practical fruit. In the first place surgeons are at work to devise methods of operation which permit the removal of the thyroid without injuring or interfering with the blood-supply of all the parathyroids. Furthermore, surgical and medical methods are studied, by means of which the evil consequences can be adequately dealt with. Surgeons abroad and in this country³⁸ are trying to develop methods of grafting the parathyroids; they have been implanted in the abdominal cavity, in the spleen and in the cavities of the long bones. The success, however, will become complete when surgeons learn to graft the organs (and the thyroids) by means of an end-to-end vascular suture by the now well-known method which was introduced into surgery, especially by the experimental work of Alexis Carrel. There are also some promising medical methods of treatment for the deficiency of the parathyroids. According to Beebe,³⁹ the nucleoproteids of the parathyroids are capable of controlling the tetanic convulsions following the removal of the parathyroids. Furthermore, MacCallum and Voegtlin⁴⁰ discovered that the postoperative spasms can be controlled by the administration of calcium. Through the investigations of Erdheim⁴¹ it was found that, in rats at least, the ablation of the epithelial bodies leads to some disturbance of the calcium metabolism. MacCallum and Voegtlin believe that the removal of the parathyroids leads to a deficiency of calcium in the body. While this theory may be incorrect, the fact is that the administration of calcium relieves the tetanic symptoms. MacCallum and Voegtlin established this fact in their experiments on animals. Calcium already has been used with success in postoperative tetany in human beings. In fact, calcium proved to be useful in the treatment of tetany in children due to other causes than the removal of the parathyroid.

Experimental medicine may well point with pride to this achievement. Little bits of tissue, the existence of which was not even known three decades ago, were recognized as organs of great importance to life and health, and medicine and surgery are already far on the road in

38. Halsted: Jour. Exper. Med., xi.

39. Beebe: Proc. Soc. Exper. Biol. and Med., iv, 64.

40. MacCallum and Voegtlin: Bull. Johns Hopkins Hosp., March, 1908; Jour. Exper. Med., xi.

41. Erdheim: Mitt. a. d. Grenzgeb. d. Med. u. Chir., xvi.

learning how to avoid their injury and how to mend the evil consequences of such injuries. It is impossible to conceive how such knowledge could have been acquired without animal experimentation.

THE SUPRARENAL GLANDS

These ductless glands were described by Eustachius in 1543. Although thus known to medicine more than four centuries, our knowledge regarding their functional significance is, as stated above, of recent date. It began with a clinical observation. In 1855 Addison described a disease which is now known by his name, in which the adrenals were found to be affected. In the following year Brown-Séquard⁴² published experiments showing that the removal of both capsules in animals leads invariably to an early death of the animal. The results of Brown-Séquard were, however, soon controverted by Phillippeaux⁴³ and by Harley,⁴⁴ who found that white rats survive the removal of the adrenals. These and other authors believed that the suprarenal capsules had no function to perform in post-uterine life and that death which sometimes followed removal of these glands was due to a stimulation of the adjoining nerves or to a peritoneal inflammation—that familiar interpretation which has obstructed the progress of many a discovery in physiology and medicine, and which was instrumental in postponing our knowledge of the significance of the suprarenal glands to life for nearly thirty years. After the revelations which came to light in the eighties regarding the importance of the thyroid glands, experiments on the suprarenal glands were taken up again by many observers. In the main the problem is now well settled; the suprarenal capsules are vital organs; after the removal of both organs from animals under most careful surgical precautions the animals die invariably at periods varying from a few hours to a few days. The most extensive and convincing series of experiments were carried out by Strehl and Weiss.⁴⁵ We know now also the reason why Phillippeaux and Harley could not confirm the observations of Brown-Séquard; the white rat possesses along its back inside the abdomen various accessory masses of cells similar to that of the supra-

42. Brown-Séquard: Compt. rend. Acad. d. Sc., 1886, xlivi.

43. Phillippeaux: Compt. rend. Acad. d. Sc., xlivi, xliv.

44. Harley: Med. Times and Gaz., 1857, p. 564.

45. Strehl and Weiss: Arch. f. d. ges. Physiol. (Pflueger's) lxxxiv, 107.

renal capsule. These accessory masses are apparently sufficient to keep up the function after the loss of the main bodies.

Many studies were also carried on with injections of extracts of the suprarenals; these injections failed to keep up the life of the animals deprived of these glands. Neither has grafting of the suprarenals proved so far a real success. The experiments with injections of suprarenal extracts, however, brought to light a great discovery. It is the now familiar fact of the various and profound physiologic effects which suprarenal extract is capable of exerting on the animal body. It ought to be stated that this discovery also came about through the initiative of a clinician. Dr. Oliver administered to patients by the mouth extracts of various organs and observed by the clinical instruments which he employed that they exerted a definite influence on the blood-vessels. After a consultation with Professor Schäfer they started a systematic investigation on animals which led to their great discovery of adrenin.⁵ We need not discuss here the great importance which this extract has attained as a therapeutic agent in medicine and surgery; it is now common knowledge.

This active extract is obtained from the medullary portion of the adrenals, secreted apparently by its specific cells. By various reactions and methods this extract has been traced, step by step, on its way from the cells to the blood in the vein of that gland. The internal secretion of this gland seems thus to have been, so to say, directly demonstrated. The cells of the medullary portion of the adrenals are similar to those found in the carotid gland, in Zuckerhandl's gland and in some sympathetic ganglia. They all have in common an affinity for chromic acid—hence the name chromaffin cells—and exert a similar physiologic action, for instance, a rise of blood pressure. The medullary portion shows also embryologically a relationship to the sympathetic nervous system. It is assumed by some⁴⁶ that the action of adrenin (adrenalin) on organs which are innervated by the dorso-lumbar portion of the sympathetic nervous system is similar to that of the action of the corresponding sympathetic nerve fibers on smooth muscle.

Reports are gradually increasing, showing the relations of the conditions of the medullary portion of the

46. See Elliot: Jour. Physiol., xxxii.

gland to various pathologic and toxicologic states (chloroform poisoning, shock, nephritis, etc.). We shall not dwell here on these details. We are in the midst of a great chapter, and the future has yet a great deal in store for our knowledge. In fact, we know as yet nothing of the significance of the cortex of the gland. But we have certainly learned a great deal about that gland in a remarkably short time. We know now that it is an absolutely vital organ, that it exerts its physiologic influence by emptying its secretion directly into the blood, and we have learned to obtain from it an extract which is of immense practical and scientific importance. These important facts have been learned by animal experimentation, and we could never have learned them in any other way.

HYPOPHYYSIS

This gland is very small, weighs about half a gram, and is hidden away in a most inaccessible manner in the sella turcica. The older anatomists ascribed to it the fanciful function of secreting mucus, hence the term of pituitary gland. In more recent times—until 1886—it was looked on as an evolutionary remnant, a sort of useless appendix of the brain. It consists of two parts, a larger anterior part, containing glandular epithelial cells, and a posterior part, which contains some nervous elements and no epithelial cells. Since Rathke (1833) and Mihalkovits (1874) it has been generally recognized that both parts are embryonically developed from different origins; the anterior part coming from the posterior pharynx and the posterior part from the midbrain.

It was again clinical medicine which began to shed light on the function of the pituitary body. In 1886 P. Marie⁴⁷ called attention to the occurrence of a new disease which he termed acromegaly and which was found to be associated with tumors of the hypophysis. The most striking sign of this disease is the overgrowth of certain parts of the skeleton, especially the extremities and the lower jaw; hypertrophy of the connective tissue is also present. The statements of Marie were confirmed by many other observers. Furthermore, it was found that gigantism, that is, an increase of growth which leads to unusual stature, is in most cases associated with tumors of the pituitary body and a concomitant enlargement of the sella turcica. These clinical observa-

47. Marie: Rev. de méd., 1886, p. 298.

tions, which clearly indicated that the pituitary gland is in some way connected with the growth of the body and exerts, therefore, a physiologic function on the growing and grown-up animal organism, led to various series of experimentation, of which we shall mention here briefly only two. In the first place, the attempt was made to study the effect of the removal of the gland. Until a few years ago these attempts seemed to be futile, as the various investigators obtained contradictory results, which was not surprising considering the immense difficulties with which the experimenters were confronted in their attempt to reach that hidden gland without endangering the life of the animal. About three years ago, however, Paulesco⁴⁸ worked out an apparently satisfactory method of getting to the pituitary body through the temporal bone. The results, which were arrived at by Paulesco himself and which were extensively confirmed, among others by Harvey Cushing,⁴⁹ seem to be uniform and reliable. Briefly stated, they are as follows: Complete removal of the hypophysis leads invariably to the death of the animal within forty-eight hours after the operation. Reaching the gland and handling it has no effect. Neither does the complete removal of the posterior part seem to have any effect. On the other hand, the complete removal of the anterior part has the same invariably fatal effect as the complete removal of the entire gland. Leaving behind a small portion of the anterior part saves the animal's life. We thus have positive evidence that the hypophysis, like the thyroids, parathyroids and the suprarenal capsules, is an organ indispensable to the life and health of the animal.

The second line of investigation, which was carried out by Schäfer⁵⁰ and his associates, by Howell⁵¹ in this country, and by many other investigators, deals with the effects of injections of extracts of the pituitary body. The results as they stand to-day are as follows: The extracts cannot save the life of the animal after removal of the gland. Extracts made of the anterior part exert no definite influence on the animal. On the other hand, extracts made of the posterior part have a definite influence on blood-pressure and, independently of the blood-pressure, also on the urinary secretion. We need not

48. Paulesco: *Jour. de physiol.*, 1907, ix.

49. Cushing: *THE JOURNAL A. M. A.*, 1909, lxxii, 249.

50. Schäfer: *Croonian Lecture, Proc. Roy. Soc., London*, 1909, lxxxii.

51. Howell: *Jour. Exper. Med.*, 1898, iii.

enter here into the details of the nature of this influence, but it is in no way comparable with the marvelous influence of the extract made of the medullary portion of the adrenals. The striking outcome of these investigations for the present is that the part which is essential to life exerts no influence by its extract, and the part which exerts such an influence seems to be unessential to life. It is evident that the action of the normal organ is not identical with the action of its extracts—a lesson which is not yet well learned by some writers who deal with the significance of iodothyron or adrenin.

With reference to the relation of tumors of the hypophysis to acromegaly and gigantism, we have at present still two contending theories. One assumes that the changes in the growth of the organism are due to a destruction or diminution of the function of the gland; the other theory assumes that the increase of growth is due to a greater stimulation of the function of the gland, assuming that the tumor, at least at its beginning, is of the nature of hyperplasia and benign in character.

As to the therapeutic application of these results, we have stated already that injection of the extract is of no avail in saving the life of the animal after the complete removal of the hypophysis. I am not aware of any attempts to graft this gland. But there is very promising beginning in the surgical treatment of the diseases due to the pathologic condition of the hypophysis. There are already on record a few successful cases of removal of tumors of the pituitary gland in which, of course, some fragments of the gland were purposely left behind. We are here only at the threshold of a new era.

Recently good results were also reported from treatment of shock, uterine hemorrhages, etc., by injection of extracts from the infundibular portion of the hypophysis.

THE THYMUS

It is true that this ductless gland gradually atrophies during extrauterine life, but it is also true that it persists for a long time after birth. With our present knowledge of the importance of the other ductless glands we are hardly justified in assuming that the thymus is a worthless fetal remnant. But we have to acknowledge that as yet there are no reliable observations or experiments which indicate clearly that the thymus has a function in postuterine life.

FACTS ESTABLISHED

Looking over the mass of facts which we have recorded in the foregoing pages, we find in the first place that the investigations of recent years have established definitely that the thyroids, the suprarenal capsules and the hypophysis are vital organs of immense importance. Furthermore, for the thyroid it was found that its extract can nearly compensate the absence of the organ. For the adrenals it was found that they furnish a very effective, therapeutically extremely important extract; this extract, however, cannot supplant the organ. The hypophysis furnishes a moderately effective extract, and this by a part which seems to be not indispensable for the life of the animal. All three glands seem to consist anatomically of two parts, of the mutual functional relations of which we know nothing definite. We know nothing of the significance and importance of the cortex of the suprarenal capsules and we know little about the posterior part of the hypophysis. We know a great deal of the importance of the newly discovered mate of the thyroids, the parathyroids, but as to the mutual relations of these neighbors we have for the present only theories, and as many as the subject permits; they are synergists, they are antagonists, and they are indifferent to one another. As to the mode by which these glands affect the life of the organism, there can be no doubt that it is accomplished by means of an internal secretion; that is, something of importance is prepared within the gland which comes in contact with the blood without the intervention of a special duct. As to the way this takes place we have again a variety of theories: each of the glands sends to the blood a specific substance which the body needs for its existence; the glands send to the blood an ingredient which neutralizes poisonous specific substances accumulated there; and, finally, specific poisonous substances are attracted to the various glands where they become detoxicated. These theoretical disagreements were and are important factors in the development of the details of our knowledge of these subjects, inasmuch as in the efforts to prove the correctness of one theory or the other a great many important facts were and are being brought to light by the supporters of the various theories.

THE INTERNAL SECRETION OF OTHER GLANDS AND ORGANS

The inspiring experimental activities in the studies of the internal secretion of the ductless glands stimulated similar investigations in other organs and brought to light the important fact that organs which have a definite function or even a definite external secretion may at the same time affect the body in a well-defined manner also by an internal secretion.

INTERNAL SECRETION OF THE PANCREAS

This became manifest especially in the discovery of the relation of the pancreas to diabetes. Here, again, clinical medicine led the way. On the basis of his own observations and those of former medical writers Lancereaux,⁵² in 1877, assumed that the so-called meager diabetes is connected with a diseased condition of the pancreas. The same view was taken subsequently by some other clinical writers. In 1889 von Mering and Minkowski⁵³ published their discovery that the complete removal of the pancreas in dogs leads to a most striking development of diabetes. The facts were soon worked out at great length by Minkowski⁵⁴ and were confirmed by numerous writers. The main facts are as follows: Complete removal of the pancreas leads to a fatal glycosuria in all animals except fowls, in which it leads only to a hyperglycemia.⁵⁵ Ligation of the pancreatic duct does not produce diabetes. The diabetes is completely prevented when one-fifth of the pancreas is left behind, no matter where this remnant is placed, provided it preserves its vascular connections with the body. Extracts of pancreas are of no avail when the pancreas is completely removed. There is no doubt that the control of the carbohydrate metabolism in the body by the pancreas is accomplished not by its external secretion, but by an internal secretion which is confined to the pancreatic gland and is thus specific. Whether this latter secretion is produced by the same cells which provide the external secretion or by a different set of pancreatic cells, for instance, the groups of cells which are known as the islands of Langerhans, is a problem which is still within the stage of theories. It was a great discovery—a sudden flash of light in that dark labyrinth of physiology

52. Lancereaux: Bull. de l'Acad. de méd., Paris, 1877.

53. Von Mering und Minkowski: Arch. f. exper. Path. and Ther., xxvii.

54. Minkowski: Arch. f. exper. Path. and Ther., xxxi.

55. Kausch: Arch. f. exper. Path. and Ther., xxxvii.

and pathology of carbohydrate metabolism. It led to numerous investigations and to the unravelling of a great amount of important detail, which, of course, we shall not attempt to discuss here. I wish only to add the remark that this great work was carried out and is being carried on essentially by modern clinicians well versed in experimental methods.

INTERNAL SECRETION IN THE ORGANS OF GENERATION

The well-known interdependence of the various organs of generation, which in the past was generally ascribed to the regulation by a nervous mechanism, is now recognized as being essentially a chemical coordination managed by the internal secretions of these organs. Instances of such chemical coordination are: the dependence of the secondary sexual characters on internal secretion of the testicles⁵⁶ and ovaries;⁵⁷ the dependence of the growth of the uterine mucous membrane in pregnancy on the internal secretion of the ovary and the corpus luteum;⁵⁸ the development of the mammary glands in pregnancy under conditions in which the activity of the nervous system is excluded; for instance, when the ovary is transplanted in the peritoneum or at the base of the ear,⁵⁹ or after the removal of the spinal cord.⁶⁰ Starling and Lane-Claypon⁶¹ succeeded in producing the development of mammary tissue in virgin rabbits by injections of extracts made of fetal tissue. The fetus while in the uterus transmits to the maternal body a substance which accomplishes two purposes: it stimulates the growth of the mammary glands and prevents the cells of these glands from resuming their specific secretion. With the removal of the fetus from the body at a period when the glands reached a certain definite stage, the glandular cells begin to secrete milk. This means that the mission of the internal secretion might sometimes consist in the inhibition of a certain function.

SECRETIN

By the discovery of secretin⁶² a new type of internal secretion came to light. Through the work of Pawlow⁶³

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- 56. Shattock and Seligmann: *Jour. Physiol.*, xxix.
 - 57. Marshall and Jolly: *Phil. Tr. Roy. Soc., London*, 1905, cxcvi.
 - 58. Fraenckel: *Arch. f. Gyn.*, 1903, lxviii.
 - 59. Ribbert: *Arch. f. Entwicklungsmechn.*, 1898.
 - 60. Goltz and Ewald: *Arch. f. d. ges. Physiol.*, Bonn (Pflüger), lxv.
 - 61. Lane-Claypon and Starling: *Proc. Roy. Soc., London*, 1905, lxxvii.
 - 62. Bayliss and Starling: *Jour. Physiol.*, 1902, xxviii.
 - 63. Pawlow: *Die Arbeit der Verdauungsdrüsen*, 1898.

it became known that the presence of hydrochloric acid in the duodenum causes a greater flow of pancreatic secretion. It was presumed that the acid produced this effect by stimulation of peripheral nerves in the duodenum and the increased pancreatic secretion was simply a nervous reflex. Bayliss and Starling, however, discovered that an extract made of the duodenal mucosa under addition of hydrochloric acid causes an increase in the flow of pancreatic juice. This extract the authors named secretin. Boiling the extract does not destroy its effectiveness. Bayliss and Starling assume that under normal conditions after the entrance of the hydrochloric acid into the duodenum a similar extract is prepared within the epithelial cells. This extract is normally given up to the circulation which carries it to the pancreas and causes the external secretion of that gland. These authors believe that secretin is the only inducing cause of pancreatic secretion. Other physiologists, however, believe that the secretion of the pancreas is also under the control of the nervous system.

It seems to me that there are well-established clinical facts which speak definitely against the sole control of the pancreatic secretion by secretin. In cases of achylia gastrica no acid is secreted within the stomach and none, therefore, reaches the duodenum; consequently no secretin can be formed. Nevertheless the digestion of various foodstuffs occurs in these patients in a practically normal way within the intestines, which, of course, would be impossible if pancreatic secretion depends exclusively on stimulation by secretin.

While secretin is thus a useful factor in the animal mechanism, its presence is not indispensable for the life and health of the animal. It may be mentioned that secretin has, in common with the extracts of the thyroids, adrenals and hypophysis, the property of not being destroyed by digestion or by heating (when not prolonged).

It is stated by Edkins⁶⁴ that also the cells of the mucosa of the pyloric part of the stomach manufacture a secretin (gastrin) which stands in close relation to the secretion of the gastric juice.

Besides the above mentioned results there are many interesting investigations which deal with the mutual relations of these various internal secretions, for

instance, the relation of the hypophysis to that of the thyroids or to that of the sexual functions, or the mutual relations of the internal secretions of the pancreas, adrenals and thyroids, and many more problems. All these investigations which we cannot discuss here open up new fields and are full of promise of scientific and practical results.

DISTINCTION BETWEEN INTERNAL SECRETION AND WASTE PRODUCTS

The internal secretions with which we have dealt so far have in common a few important characteristics which ought not to be lost sight of. In the first place, all these secretions are traced to organs which are provided with definite secretory elements. In the second place, there are good reasons for assuming that in each of these organs the respective secretions are the main products of the specific affinity of the secretory elements and not by-products (waste) secondary to another, chief activity of these elements. Furthermore, each secretion is specific for each organ. For instance, antitetanic activity is exercised only or essentially by the parathyroids, and glycolysis only or essentially by the pancreas.

However, the term internal secretions, as it was introduced by Brown-Séquard in 1891⁶⁵ and as it now frequently used, is meant to cover also a variety of products which have in common with the before mentioned secretions only the fact that they are carried away from the place of their production through the blood or lymph capillaries and not by special ducts. It is true that the waste products of the testicles, of the kidneys, of muscles, and of other organs and tissues, which are thus included under the term of internal secretion, have, of course, to get first into the circulation before they can be eliminated from the body. And it is further true that, since they have to linger a little while within the organism before they can be completely eliminated, the fluids and tissues of the animal body become somewhat adapted to them and often form definite reactions to protect the body against their deleterious influence. But while by the presence of such reactive mechanisms the impression is created that these waste substances are integral parts of the living organism, the fact should not be lost sight of that they are poisons, harmful to the body, and that the mechanism of the body with regard to them is

65. Brown-Séquard: Arch. de physiol. norm. et path., 1891.

arranged to defend it against them, to neutralize their poisonous effects and to hasten their removal from the body. What logical and practical advantage can there be in the attempt to class these waste products together with the internal secretions with which we have dealt before? It is probable that the very aim of some of these secretions is to protect the body against some of these waste products.

Let us take CO₂, a waste product of the importance of which recently a great deal has been said and written. When muscles are contracting CO₂ is formed. This gas, however, is not secreted by the muscle cell and its production is not the functional object of the muscle fiber; it is here only a secondary, a waste product. This gas is produced also by the activity of any other cells, for instance, in the secretory activities of the glands. It is not secreted by them, either, and its production is not the function of the gland cell; it is here also merely a waste product. Its production is, therefore, not confined to any specific cell, tissue or organ. In the assumption of Bohr that CO₂ is secreted by the epithelial cells of the pulmonary alveoli, the term secreted is simply misapplied; it is meant that there is a vital action in the removal of the gas. A cell secretes only what is new; the epithelia of the alveoli do not create CO₂; they only hasten its removal by some vital action. That these epithelia, as well as the endothelia of the capillaries, are provided with such vital power demonstrates that the organism is provided with special mechanisms for the speedy, infallible removal of that gas, the most deleterious waste product. Now a great deal of stress has been laid on the theory or fact that the respiratory center is greatly stimulated by CO₂. What does this specific irritability of the respiratory center signify? Again, nothing else but that the body protects itself by making the respiratory center so sensitive and so reactive against this dangerous waste product that any surplus of it automatically sets going a well-working mechanism for its rapid elimination. That the animal organism is provided with sensitive mechanisms for the effective removal of a substance can surely not be taken as an evidence of the necessity and importance of this substance to the life and economy of that organism. We know now that the animal organism is provided with numerous effective defences when invaded by bacteria or other foreign injurious substances. Will any one claim that the existence

of these well-organized means of defence within the body is a proof that these bacteria or deleterious substances belong to the economy of the animal body? The animal possesses, on one hand, a variety of organs to provide it with certain specific products (secretions) to maintain its life, and, on the other, it possesses various other mechanisms for the purpose of maintaining life by the effective removal of other products? Can the contrast between the two kinds of products be greater? I cannot see that any progress can come from a generalization which tries to unite such heterogeneous products under one head. It is only capable of obscuring the issue. At any rate I would strongly advocate confining the term internal secretion to specific secretions of organs which are provided with definite secretory elements.

SUMMARY

Let us now summarize the main facts of importance we have learned in the recent experimental studies connected with the problem of internal secretion.

1. It became established that the thyroids, suprarenal capsules and hypophysis are vital organs, the removal of which means ruin to the animal organism. Only three decades ago they were considered as useless remains.

2. Little bits of definite tissue, the parathyroids, were recognized as vital organs, the removal of which is fatal to the animal. Their very existence was completely unknown thirty years ago.

3. New diseases were recognized in connection with the impairment of these organs: myxedema, acromegaly, etc.

4. The real nature of cretinism was recognized.

5. Great theoretical and practical lessons were learned with regard to extracts prepared from these ductless glands; the results are of considerable theoretical and practical importance. We need only refer to the striking effect of the thyroid extract in the treatment of natural and artificial (surgical) myxedema and cretinism, and to the great usefulness of adrenalin in hemostasis, or in sthenic conditions. Valuable practical therapeutic results were recently obtained also from the extract of the hypophysis.⁶⁶ There is no doubt that even from a purely therapeutic point of view the lessons learned in this short period of three decades by the methods of

experimental medicine compare favorably with all the lessons learned in therapeutics by the empirical method for many past centuries.

6. It was discovered that organs with a definite external secretion may exert also another function by means of internal secretion. Especially important was the discovery that the removal of the pancreas leads to diabetes. In the innumerable observations dealing with the exasperating problem of diabetes this discovery is an immense step forward, although the goal is not yet in sight.

7. A new type of correlation by means of internal secretion was learned, namely, that organs participating in a common complex function are capable of controlling their coordination by means of an internal secretion: the interrelations of the organs of generation and the relations of the duodenum to the secretion of the pancreas (secretin).

8. An important lesson was learned, that the organs which exert an influence on the mechanism of the body by means of an internal secretion are provided with an abundance of factors of safety; that is, they possess of the specific vital tissues a good deal more than the animal needs for its immediate maintenance.

9. Surgery learned many valuable lessons. In the first place it learned that radical operations on these organs are invariably ruinous to patients. It learned further, however, that a favorable result can nevertheless be obtained by leaving in the body a comparatively small vascularized fragment of the organ. Surgeons have learned the difficult task in removing goiters of avoiding interference with the parathyroids and their vascular supply; they are learning how to reach and remove tumors of the hidden hypophysis, and they are learning to mend the evils of an unavoidable radical removal of one of these organs by grafting such an organ or a fragment of it in various safe places in the body.

These results surely mark an immense scientific and practical progress. Remembering that it was made within a brief period of less than three decades, and remembering further the dense ignorance which reigned in this field for centuries, even the most superficial observer must admit that the progress is truly marvelous. Furthermore, the observer must readily admit that the acquired results are not luxurious contributions to

abstract science, but consist of elementary indispensable knowledge in the domain of medicine.

THE LESSONS TAUGHT

There are many valuable lessons that we may and ought to learn from the history of this chapter of modern medicine.

In the first place nearly every fact of importance in this chapter, as was pointed out before, was learned by the purely biologic method of research, and experimentation on animals had the lion's share in it. It is self-evident that none of the fundamental facts could have been discovered by any other method.

Furthermore, the results were achieved largely through the harmonious cooperation of medicine, surgery and experimental medicine. Experimentalists and physiologists should remember that it was the observation of the clinician Addison which set Brown-Séquard to work experimentally on the suprarenal capsules; that it was the clinical observations of Oliver which led to the discovery of adrenin by Schaefer and himself; that it was the observations of the clinicians Gull and Ord, on one hand, and of the surgeons Kocher and Reverdin, on the other, which contributed greatly to the establishment of the vital importance of the thyroids; that the clinical observations of Marie led to the recognition of the hypophysis as a vital organ; that the clinical statements of Lancereaux and others were the forerunners of the experimental discovery of the internal secretion of the pancreas. The physiologists should also remember that it was Schiff and Brown-Séquard who were instrumental in the establishment of the vital importance of the ductless glands, experimenters who did not enjoy the full approval of the official physiologists of their time, and that most of the experimental work on internal secretion was at least first carried on essentially by experimental clinicians and surgeons, and that such eminent physiologists as Munk and Pflüger were and still are fighting the teachings of internal secretions, which can be explained only by the deep-rooted distrust of physiologists of the mechanical school of any results obtained by purely biologic methods.

It deserves to be pointed out that some of the results owe their origin to mere hypothesis. It was the hypothesis of Felix Semon of the similarity of the phenomena in the clinical observations of Ord and the surgical

results of Kocher which led to the formation of the committee of the London Clinical Society, and it was the report of this committee which definitely established the importance of the thyroid to life. The hypothesis of Gley of the relations of the parathyroids to the thyroids, though probably incorrect in its original conception, led to the establishment of the fact of the antitetanic function of the parathyroid.

On the other hand, it ought to be evident that neither hypothesis alone, nor even clinical or surgical observation, is capable of uncovering the whole truth. Mere observations and ingenious hypotheses give the stimulus and create the problem; its solution can be hoped for only by animal experimentation. Sometimes surgery initiates also a solution of the problem; but we must keep in mind that when surgery teaches a lesson it has already made an experiment, and often a futile one, on a human being! The history of the radical operation for goiter should be a lesson to all surgeons that progress in surgery must be preceded by animal experimentation; otherwise it may sometimes mean ruin to human life.

The experimental history of the ductless glands teaches us the impressive lesson not to rely on a few experiments, or on experiments made only on one species of animals, or carried out by only one experimenter. The experiments made by Phillippeaux and by Harley on white rats postponed the discovery of the vital importance of the suprarenal capsule for thirty years. Contradictions between experimenters should not discourage further investigation; on the contrary, it often indicates the presence of an important fact not even looked for. Neither should an apparently satisfactory solution prevent us from reinvestigating the problem. When the chapter on the thyroid seemed to come to a beautiful close by the discovery of the curative effect of its extract, it surely appeared to many that the problem was satisfactorily solved. Nevertheless further experimentation disclosed soon the surprising fact that in all the foregoing experiments and observations two organs instead of one was dealt with. Re-examination of seemingly well-established facts is one of the best means to further scientific progress.

For hundreds of years the functions of the ductless glands were shrouded in deep mystery. In less than three decades a flood of light was shed on these and allied functions by animal experiments in harmonious cooperation with medical and surgical observations. Can any person with a sane judgment be in doubt as to the usefulness of modern experimental medicine?

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Animal Experimentation in Relation to Protozoan Tropical Diseases

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"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—Charles W. Eliot.

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ANIMAL EXPERIMENTATION IN RELATION TO PROTOZOAN TROPICAL DISEASES

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PASTEUR'S INVESTIGATIONS

The investigations of Pasteur¹ proving that the disease of silkworms known as pebrine is due to infection by a living agent had the immediate practical result of restoring the languishing silk industry of France and Southern Europe, and also produced the greatest interest by the demonstration that disease can be produced in animals by infection with a microbe. The fact that the infectious agent is a protozoon received little attention, and for many years following Pasteur's discovery bacteria furnished the main object of medical investigation; only recently have numerous researches begun to reveal the frequency with which protozoa occur as parasites in man and the lower animals.

But if the expansion of the subject of parasitic protozoology is recent, the recognition of the tropical diseases, as a separate group, is even newer, and, in spite of the extremely rapid growth of our knowledge of these diseases, we must still regard the subject as relatively undeveloped. This being the case, the results hitherto obtained from experiments and investigations in tropical protozoology are to be regarded as hardly more than foreshadowing those which may be expected from further research.

ANIMAL STUDY UNAVOIDABLE

In considering the part played by animals in the development of our knowledge of tropical diseases of protozoan origin, several lines of thought present themselves. In the first place, the parasites causing these dis-

1. Pasteur, L.: Rapport, etc., relativement à la maladie de vers à soie, Paris, 1868; Pasteur, L.: Etude sur la maladie de vers à soie, Paris, 1870.

eases are themselves members of the animal kingdom, and the study of any of them involves a measure of animal experimentation. In the second place, in many instances the protozoan parasites causing diseases are carried from one individual to another by insects. The study of the insect carriers of disease and of the life history of the parasite in the insect again involves a certain sort of animal experimentation, the insect being the subject of experiment. Furthermore, most of our information concerning the protozoan parasites has been acquired from studies of protozoa spontaneously infecting the lower animals, and studies of these infected animals may be classed as animal experimentation. Finally, laboratory inoculations of protozoa into healthy animals have been made with varying success. This article will deal mainly with the two last-mentioned groups of animal studies, but it will be necessary to include clinical and zoologic researches in order to give a connected account of the progress in our knowledge of the diseases under consideration.

The tropical protozoan diseases have become recognized as a group only after many independent and apparently unrelated studies. The circuitous course of these studies may be suggested by mentioning a few of the important ones, such as those of Pasteur, in France, on pebrine; of Lösch, in Russia, and Kartulis, in Egypt, on amebic dysentery; of Laveran, in Africa, on malaria; of Smith and Kilborne, in the United States, on ticks as carriers of Texas fever; of Evans, in India, and Bruce, in Africa, on trypanosomiasis in animals; of Ross, in India, on the transmission of malaria by mosquitoes; of Dutton and Todd, in Africa, on sleeping sickness, and of Schaudinn, on the identification and properties of numerous protozoa.

AMEBIC DYSENTERY

The principal facts relating to amebic dysentery with which we are acquainted have been learned from clinical and pathologic studies. Owing to the difficulties encountered in growing the amebas and in reproducing the disease in lower animals in a manner which excludes the possible action of bacteria, there are a few who still find room for doubt as to the exact relation of amebas to human disease, although most authorities accept it as proved that at least one type of ameba produces dysentery in human beings.

Lambl observed amebas in human fecal matter, but they were not regarded as pathogenic until Lösch² described the ameba and the disease now known as amebic dysentery. After administering amebic discharges to four dogs, by mouth and rectum, Lösch found amebas in the stools of one of them, in whose rectum also there were numerous amebas accompanying inflammatory and ulcerative changes. Lösch could not assign a specific etiologic rôle to the amebas, but thought it probable that they played a secondary part in producing the disease. The intestinal bacteria complicated the experiments, which were all the more difficult, since the amebas could not be grown in pure culture and their specific action be observed.

STUDY OF AMEBA

Clinical and pathologic reports, such as those of Osler,³ Stengel, Musser, Dock, and Councilman and Lafleur,⁴ established amebic dysentery as a clinical entity, but amebas were nevertheless frequently found in the stools of persons free from any symptoms of dysentery. Kartulis,⁵ stimulated by certain observations made during Koch's cholera expedition to Egypt, made a careful study of the dysenteric conditions in Alexandria. From a study of over 500 cases, he concluded that amebas are responsible for a characteristic form of dysentery, and that they are also the cause of the liver abscesses often complicating the disease. Kartulis did not succeed in his early attempts to produce experimental amebic dysentery in monkeys, cats, dogs, rabbits and guinea-pigs, but later produced typical forms of the disease by giving to young cats rectal injections of amebic discharges. He also claims that he grew amebas from liver abscesses in pure cultures in straw infusion, and with these cultures successfully inoculated cats, the animals dying from a typical amebic dysentery. Inoculation with bacteria and with dysenteric stools freed from amebas never caused dysentery in his experimental animals. No other experimenters have been able, however, to repeat Kartulis' experiment of growing amebas in pure culture, although Kruse and Pasquale have produced dysentery by injections of ameba-containing pus from liver abscesses.

2. Lösch : Virchows Arch. f. path. Anat., 1875, xlv, 196.

3. Osler : Bull. Johns Hopkins Hosp., 1889, i.

4. Councilman and Lafleur : Johns Hopkins Hosp. Rep., 1891, ii.

5. Kartulis : Centralbl. f. Bakteriol., 1891, ix, 365.

MODE OF INFECTION

Although human beings probably never receive infection through the rectum, Kartulis' experiments at least placed the subject on a more substantial basis, and subsequent experiments have shown that amebic dysentery can result after swallowing amebas. The ordinary, free and unprotected amebas fail to produce the disease after being swallowed, as they are destroyed in the upper part of the digestive tract by the digestive juices. Under certain conditions, however, the amebas become encased in cysts, which protect them from the digestive juices and other injurious agents. In this encysted condition amebas can pass through the stomach and upper intestine unharmed, and on arriving at the lower part of the intestine can grow out into the usual free form and give rise to amebic dysentery. That encysted amebas taken by mouth can set up amebic dysentery was shown, in the case of human beings, by Calandruccio, and, in the case of animals, by Quincke and Roos,⁶ Kruse and Pasquale,⁷ H. F. Harris,⁸ Jürgens,⁹ Musgrave and Clegg,¹⁰ and others. As a further proof of the specific action of amebas, Harris, in dogs, and Marchoux¹¹ in cats, which survived the infection for fifteen or sixteen days, observed the development of liver abscesses—a very dangerous and characteristic complication met with in human beings suffering from chronic dysentery.

Although clinical and pathologic observations and the experiments referred to would seem to establish the fact that the ameba is a disease-producing agent, the question was far from being closed. Many experimenters failed to confirm the results just outlined, and in addition the conditions of some of the experiments were too severe to make the positive cases convincing. Moreover, forms of infectious dysentery occur in which amebas are not present. Light was thrown on this group of cases by Shiga's demonstration of a bacillus as the cause of

6. Quincke and Roos : Berl. klin. Wchnschr., 1893, xxx, 1089.

7. Kruse and Pasquale : Ztschr. f. Hyg. u. Infektionskrankh., 1894, xvi, 142.

8. Harris, H. F. : Virchow's Arch. f. path. Anat., 1901, lxvi, 67.

9. Jürgens : Ztschr. f. exp. path. u. Therap., 1907, iv, 769.

10. Musgrave and Clegg : Pub. of the Bureau Govt. Lab.. Biol. Lab., Manila, P. I., 1904, No. 18; Musgrave and Clegg : Philippine Jour. Sc., November, 1906, i, 909-950. [Musgrave and Clegg have found that amebas can be grown in cultures, if suitable bacteria are growing on the same culture media. They obtained growths of amebas from raw vegetables, water, and dysenteric discharges, and report that they produced abscesses and various amebic infections with cultures from all sources.]

11. Marchoux : Ann. d'hyg. et de méd. coloniales, 1900, iii, 129.

numerous cases of epidemic dysentery. The widespread occurrence of dysenteries of bacterial origin has been shown by reports of Flexner, Strong, Lentz, Kruse and many other writers all over the world.

Again, it has been found that amebas are frequently present in the stools of persons who have no symptoms of dysentery; Schaudinn finding them in the stools of from 20 to 66 per cent. of non-dysenteric persons. This has led to the view that there are various kinds of amebas, or that there is at least one pathogenic ameba and at least one harmless type. Most writers hold to the view that there are at least two types, and, while many believe that the types can be differentiated by their microscopic appearance,¹² Musgrave and Clegg maintain, as the result of their experiments, that there is no ready means of distinguishing harmless amebas from those that produce disease, and intimate that all amebas are pathogenic. Schaudinn¹³ has helped to clear up the situation by showing that there are at least two types of intestinal amebas, distinguished by differences in their manner of growth and reproduction, and his classification and conclusions based on the differences in the life of the two amebas are the ones generally accepted at the present day.

FURTHER STUDY OF AMEBAS

The anatomic changes produced by amebas have been studied in man, but the early and significant stages of the diseases can be seen only in experimental animals. The manner in which the amebas penetrate into the intestinal glands and lead to destruction of the tissues has been described by Jürgens, Quincke and Roos, H. F. Harris and Kruse and Pasquale.

While studies on man and animals indicate that the ameba produces a dangerous disease, there are still many problems remaining unsolved. The conclusions of Schaudinn must be confirmed; the various pathologic and non-pathologic conditions in which amebas occur need further study; although amebas have been found in the mouth and in abscesses of the jaw, and spontaneous amebic disease has been found in animals (Strong), the characteristics of these parasites and the number of species of pathogenic amebas should be established. We

12. Craig: Jour. Infec. Dis., 1908, v. 324.

13. Schaudinn: Arb. a. d. k. Gesndhtsamte., 1903, xix, 547.

know very little at present of methods of protection against this infection and very little of the life of parasitic amebas outside of the body. In the elucidation of such problems—all connected with the welfare of human beings—animal experimentation will almost certainly be necessary.

TEXAS FEVER AND ALLIED DISEASES

In 1891-2 Smith and Kilborne¹⁴ discovered and proved that Texas fever, a destructive disease of cattle, is due to infection of the blood by a minute pear-shaped parasite, often occurring two by two in the blood corpuscles, and named by them *Pyrosoma bigeminum*.¹⁵ Smith and Kilborne performed a work of epochal importance. Not only did they discover the cause of Texas fever, but they explained how it happened that the disease was spreading gradually northward over an ever-widening area. At a time when the relation of insects to disease was hardly suspected, they proved that the parasite of Texas fever is taken up by ticks which bite the diseased animal. The tick, when gorged with blood, drops off and lays an enormous number of eggs which harbor the infection. The eggs develop into young forms of tick, which die unless a chance is offered to suck blood. If the larval ticks have a chance to feed on cattle which have come from a region free from Texas fever, the disease is transmitted to the cattle. It was through the agency of infected ticks' eggs that Texas fever was slowly being carried northward over the country. This series of experiments furnished the first proof that blood-drawing vermin, such as ticks, can be carriers of a microbial disease, and thereby brought to light a method of infection hardly dreamed of previously, but now known to be characteristic of a large group of protozoan diseases.

Several other diseases caused by parasites of this genus have been discovered in sheep, in dogs, in horses, in rats, in monkeys, in goats and asses, and a similar disease in man has been described. A great many experiments have been undertaken with the parasites of these diseases in attempts to gain a clear knowledge of the different stages in their development and of the peculiar mechanism by

14. Smith and Kilborne: 8th and 9th Ann. Rep. of Bur. An. Indust. U. S. Dept. Agric., 1891, 1892, pp. 177-305.

15. There has been much discussion over the name of this parasite. It is most widely known as *Piroplasma bigeminum*, but it is now claimed that according to the rules of nomenclature, *Babesia bovis* displaces the name given by Smith.

which the diseases are spread, but the problems have not yet been thoroughly elucidated.¹⁶ These parasites have been grown by Miyajima¹⁷ and Martini;¹⁸ nevertheless their characteristics must be studied in the living body, and it is clear that progress in understanding diseases of this type and in combating them cannot be expected except through the employment of animal experimentation. Without referring to the direct bearing of Smith and Kilborne's experiments on the cattle-raising industry, it may be pointed out that their work furnished a clue of crucial importance in a flood of investigations on other diseases, which already have been, literally, of inestimable value to human welfare.

MALARIA AND ALLIED DISEASES

In order to gain any conception of the immense change that has been brought about by studies on malaria it is necessary for us to contrast the prevalence of the disease to-day with that of twenty-five or thirty years ago, and to take note particularly of the attitude of mind which commonly prevailed in regard to it. The present improved state of affairs, in which malaria is being successfully combated and has been made a preventable disease, is the outcome of protracted studies of apparently disconnected matters, such as microscopic studies of the blood of malarial patients; inoculation experiments on animals, and even on man; the study of blood diseases in birds, field mice and other animals; the study of the classification, anatomy, distribution, habits, breeding-places and life-histories of mosquitoes. From such varied sources contributions have accumulated until most of the former mysteries connected with malaria have disappeared, and there are now few diseases concerning whose origin and spread we have such clear knowledge.

LAVERAN'S DISCOVERY OF PARASITES

When Laveran¹⁹ first described the malarial parasites, in 1880, the attention of the medical world was beginning to focus on bacteria as disease-producing agents, and it was several years before the importance of Lav-

16. The recent works on this subject are excellently reviewed in Calkins' *Protozoology*, 1909.

17. Miyajima: *Philippine Jour. Sc.*, Sec. B, May, 1907, No. 2, ii, 83.

18. Martini: *Philippine Jour. Sc.*, Sec. B, June, 1909, No. 3, iv, 147.

19. Laveran: *Bull. de l'Acad. de med.*, Paris, Nov. 23, 1880, ix, 1235; Laveran: *Compt. rend. Acad. d. sc.*, 1881, xciii, 627.

eran's discovery was recognized and its accuracy established. However, the work of the Italians, led by Marchiafava and Celli and Grassi, and of American clinicians such as Osler and Thayer, soon placed beyond question the fact that the bodies described by Laveran are parasites and that they are present in the red-blood corpuscles of patients suffering from malaria. In the flood of investigations made on the blood of malarial patients, it was soon learned that healthy human beings can be infected by inoculating them with malarial blood,²⁰ and that there are several types of malarial parasite, producing different effects in man. One, the parasite of tertian malaria, causes chills every other day; a second causes chills at 72-hour intervals (quartan malaria); a third causes irregular chills and is responsible for what is known as pernicious or tropical malaria. These types can be distinguished from each other by microscopic examinations.

LIFE CYCLE OF PARASITE

Golgi,²¹ during 1885-6, traced the stages in the growth of the quartan and tertian parasites from the time that the minute form enters the red-blood corpuscles, through different periods of development, up to maturity, when the full-grown form divides into segments, each of which enters a fresh red corpuscle to repeat the process. He showed that the malarial chill corresponds to the time when one generation of full-grown parasites is simultaneously segmenting. In 1891 Marchiafava and Celli made a similar study of pernicious malaria. About this time Danilewsky²² investigated a number of warm-blooded and cold-blooded animals and found several kinds of blood parasites, among them one in birds which resembles that of human malaria.

MOSQUITO AS A CARRIER

The works referred to established a relationship between the parasite found in the blood of human beings and the disease, and the occurrence of a similar parasite in birds, but there was no clue to indicate where the parasite came from nor how it got into the blood, nor was there any generally accepted explanation of the mode

20. Thayer and Hewetson: Johns Hopkins Hosp. Rep., 1895, v, 35-39 and 53.

21. Golgi: Arch. p. le sc. med., 1885, No. 4; Golgi: Gaz. d. osp., 1886, No. 53.

22. Danilewsky: Ann. de l'Inst. Pasteur, 1890, No. 7, pp. 427, 753.

of infection.²⁰ It is true that Laveran supposed that the mosquito was concerned in some way in this transfer, and that this idea occurred independently to Manson, who had found mosquitoes active in the spread of a blood disease caused by a minute parasitic worm (*Filaria bancrofti*).²³ Manson suggested that the malarial parasites were carried by mosquitoes from malarial patients; that the mosquitoes infected drinking-water, which in turn carried the parasite to susceptible persons. Bignami also supposed that the malarial organism passed part of its life in the external world, where mosquitoes in some way picked it up and inoculated the human being in the act of biting him. The mosquito hypothesis, however, lacked support until 1895, when Major Ronald Ross,²⁴ a medical officer in the Anglo-Indian service, observed that the malarial parasites, taken from a patient into the stomach of a mosquito, underwent interesting changes, with the production of flagellated and spherical forms, which were subsequently found by MacCallum²⁵ to be sexual forms of the protozoan. In many attempts to continue the study Ross failed until he employed a special type of mosquito, now known to be the *Anopheles*, with which he confirmed his previous finding. Directing his attention to bird malaria, Ross discovered that if certain types of mosquitoes suck blood from infected birds, the parasite, *proteosoma*, enters the mosquito, passes through an elaborate cycle of changes, and after about 9 days develops into forms which accumulate about the proboscis of the mosquito and are discharged into the next bird attacked by the insect, to reproduce the disease afresh. Ross succeeded by this means in infecting healthy birds.

The bearing of Ross' discovery on the problem of human malaria was apparent, and immediately the study was taken up by the Italian workers who proved that the mosquito plays the same rôle in this disease as in bird malaria. In arriving at this result, the study of malarial diseases of field mice and lower animals and a painstaking study of mosquitoes by Grassi, played a part.

23. King : Insects and Diseases ; Mosquitoes and Malaria, Pop. Sc. Month., 1883, xxiii, 644.

24. Ross : Lancet, Dec. 18, 1897, and Feb. 26, 1898 ; Ross : Ann. de l'Inst. Pasteur, 1899, No. 2.

25. MacCallum : Jour. Exper. Med., 1898, No. 1, iii, 125.

The chief workers among the Italians were Grassi, Bignami and Bastianelli.²⁶

CYCLES OF GROWTH AND REPRODUCTION

From these investigations it developed that the malarial parasites have two cycles of growth and reproduction: in the warm-blooded animal reproduction is asexual; in the mosquito sexual reproduction occurs. Both cycles are necessary for the perpetuation of the malarial parasite. At this point in the investigations it became urgently necessary to determine whether any other animal resembles man in its capacity to harbor the malarial parasites. Experiments on this point were perfectly uniform in their results;²⁶ neither by inoculation of animals nor by having them bitten by infected mosquitoes was it possible to cause the parasites of human malaria to grow in their blood. The uniformity of these results gave assurance that the lower animals do not suffer from human malaria and that they are not concerned in the spread of the disease. It may be remarked, however, that diseases resembling malaria, but specific for certain types of lower animals, have been observed by Kossel, Ziemann, Koch and Vassall.

ANOPHELES MOSQUITO

The adjustment of the malarial parasites to their environment is very delicate; a certain stage of the parasite of human malaria will survive and multiply in mosquitoes of the genus *Anopheles*, but will not survive in other mosquitoes; the parasite of bird malaria will not survive in *Anopheles* mosquitoes, but survives and multiplies in *Culex* mosquitoes. The parasites of bird malaria do not live in human blood, even if introduced artificially or by an infected *Culex* mosquito, and the parasites of human malaria cannot live in other animals. Various other mosquitoes have been found to be capable of carrying malaria to human beings, nearly all being of the genus *Anopheles*, and it is now known that many genera of mosquito are quite incapable of carrying the disease.

It has been proved that the mosquito is not simply a passive carrier of the malarial parasite, but that the parasite invades the tissues of the mosquito and passes

. 26. Grassi: Bignami, Bastianelli, Dionisi, etc., Rev. Acad. dei Lincei, Nov. 28, 1898 to May 1899; Reviewed by Ziemann: "Malaria" Mense's 'Handb. d. Tropenkrankh.,' iii, Parts 1 and 2.

through certain complicated stages of development before arriving at a condition in which it is capable of infecting a fresh human subject. The changes which the parasite undergoes in the mosquito are apparently essential to the continued existence of the parasite, and we must conclude that the malarial organism is regularly parasitic for two living creatures—man and the *Anopheles* mosquito, and that it can continue to live and multiply only when it can occasionally pass from one of these hosts to the other and back.

The complicated and elaborate stages in the development and reproduction of the malarial parasite, both in man and the mosquito, have been worked out step by step. Grassi,²⁶ in 1901, studying pernicious or estivo-autumnal malaria; Schaudinn,²⁷ in 1901, the form causing tertian malaria. Schaudinn observed the parasites obtained from the proboscis of the mosquito enter human red-blood corpuscles, and thereby completed the chain of evidence required to prove conclusively that the mosquito parasite is the cause of human malaria.

DISAPPEARANCE OF MALARIA

The application of the facts learned by these studies has led to most remarkable changes in modern life. As soon as it became clear that man cannot acquire malaria except through the bite of a mosquito, and that the mosquito can become infected only by biting a malarial patient, the prevention of malaria and its eradication at once became a problem to be attacked by exterminating *Anopheles* mosquitoes and by preventing them from gaining access to malarial patients.

The salutary effect of the antimosquito campaign in decreasing the death-rate and sick-rate from malaria has quite fulfilled all predictions. The banks of the Suez Canal have become habitable; the Roman Campagna is losing its terrors; the construction of the Panama Canal has been made possible, and life in the tropics has been robbed of one of its greatest dangers, largely through the works of Laveran, Ross and Grassi. Moreover, the knowledge acquired has not only led to an intelligent campaign against malaria, but it has been of value in understanding other dangerous diseases carried by insects.

27. Schaudinn: Arb. a. d. k. Gsndhtsamte., 1902, xviii, 169.

YELLOW FEVER

It will be recalled that up to a very short time ago the southern and eastern ports of this country frequently were in danger from epidemics of yellow fever. The cause of the disease was unknown, its manner of spread mysterious, its mortality high, and the dread of its appearance was constantly recurring. In 1900, five years after Ross discovered that malaria of birds is transmitted by mosquitoes, an American commission²⁸ made an elaborate investigation of yellow fever. The disease could not be conveyed by contact, nor by the ordinary channels through which bacterial diseases spread, and experimental animals could not be infected. The blood from patients was inoculated into non-immunes and they promptly developed yellow fever. Mosquitoes of the genus *Stegomyia* were allowed to bite susceptible persons after sucking blood from yellow fever patients, and the disease was transmitted after a number of unsuccessful attempts. The first person on whom this experiment succeeded was Dr. Carroll, one of the members of the commission, and a few days later Dr. Lazear, also a member of the commission, allowed himself to be bitten, contracted yellow fever and died. In spite of numerous and careful attempts, no other method could be found which could be supposed to play a part in the natural spread of yellow fever, and the commission concluded that victims regularly are inoculated from infected *Stegomyia* mosquitoes, a conclusion which has been abundantly confirmed. It has since been shown by Marchoux and Simond that the offspring of infected mosquitoes can transmit a mild form of yellow fever.

The most painstaking investigations have failed to demonstrate the virus of yellow fever, and there is reason to believe that it is too small to be seen even with a microscope. In spite of the fact that the germ of the disease is unknown, the work of the American commission has demonstrated that yellow fever will not spread in a community unless infected *Stegomyia* mosquitoes occur. The truth of this theory has been tested on a grand scale. In Havana the destruction of mosquitoes and the screening of yellow fever patients have relieved the town of the scourge. The same measures proved

28. Reed Carroll, Agramonte and Lazear: Philadelphia Med. Jour., 1900, vi, 796; Reed, Carroll, and Agramonte: THE JOURNAL A. M. A., 1901, xxxvi, 431.

sufficient in New Orleans some five years ago, and have given equally satisfactory results at Panama.

TYPHUS AND DENGUE

Typhus fever and dengue, two diseases whose virus is still unknown, have been studied in much the same manner. In the case of dengue, Ashburn and Craig²⁹ concluded that the disease is transmitted by the ordinary *Culex* mosquito; in the case of typhus, Vassall finds that the blood of patients will convey the disease if inoculated into susceptible individuals, but he has not yet determined what biting insect is the carrier.

In 1903 minute bodies were found in the cells of victims of one of the obscure fevers of India, known as "kala-azar,"³⁰ or "dum-dum fever." This disease, confused with malaria for many years, was finally recognized as one of the scourges of India, where it has practically destroyed villages by its widespread and high mortality. The bodies found by Leishman³¹ and Donovan³² in kala-azar patients appeared to be the infectious agent causing the disease. The studies of Rogers and Patton³³ have shown that this disease also is carried by an insect. It has been found that bedbugs which have bitten patients with kala-azar have the protozoon in their stomachs, and it has been learned that the parasite undergoes development in the insect. Up to the present time the complete life history of the parasite has not been traced, and we do not know what becomes of it, nor how it gains entrance into human beings. The fact that the disease cannot be given to experimental animals increases the difficulties of study.

RESULTS OBTAINED

It can be seen from this brief review that an enormous amount of research work has been devoted to the study of malaria and related subjects during the last thirty years. There can be no doubt that our ideas concerning the nature of malaria and yellow fever, and our practices in dealing with them, have been profoundly modified by the discoveries of research workers. It is equally certain

29. Ashburn and Craig: Philippine Jour. Sc., Section B, 1907, No. 2, ii, 128.

30. Leishman: System of Medicine, Allbutt and Rolleston, Part 2, ii, 226.

31. Leishman: Brit. Med. Jour., May 30 and Nov. 21, 1903, i.

32. Donovan: Brit. Med. Jour., July 11, 1903, ii, 79.

33. Patton: Scientific Memoirs by the Officers of the Medical and Sanitary Departments of the Government of India, 1907, No. 27.

that the workers have been justified by the results attained; waste places have been made habitable; the conditions of human intercourse, welfare and health have been improved, and there has already been an incalculable saving in human life through the preventive measures now so well known. It would be as improper to assert that these results could have been attained just as readily without animal experimentation as to claim that they resulted solely from such experimentation. The use of experimental animals was, however, necessary—just as necessary as the study of sick patients; just as necessary as the study of mosquitoes. It is highly probable that the mastery over malaria and yellow fever would not have been obtained if studies on animals had been done away with thirty years ago.

SLEEPING SICKNESS AND ALLIED DISEASES

As far back as 1841 Valentin described motile protozoa in the blood of salmon. Similar actively moving bodies were found in frogs by Meyer and received from Gruby the name "*Trypanosoma sanguinis*." Little attention was paid to these parasites for forty years, and, although found in the blood of various lower animals, they were not regarded as disease-producing agents. In 1879 Lewis reported the occurrence of trypanosomata in the blood of Indian rats. A short time later Evans discovered parasites of the same character in the blood of animals suffering from the fatal Indian epizootic "surra," and, as the result of his studies, concluded that surra is caused by the trypanosoma. The disease proved uniformly fatal for horses, mules and dogs; camels were much less susceptible, while oxen could recover after inoculation with the parasite.

About 1895 Bruce³⁴ was sent to study "nagana," a highly destructive disease of animals in South Africa, and found the animals infected with a parasite like that described by Evans in surra. He inoculated horses and dogs with the blood of cattle suffering from nagana and reproduced the disease.

TSETSE FLY THE CARRIER

In attempting to trace the manner in which animals became infected, Bruce was impressed by the fact that nagana has a very definite localization, occurring

34. Bruce: Osler's Modern Medicine, 1907, I, 460.

with frequency in certain regions, being absent from others. It prevailed in regions inhabited by a stinging fly, the "tsetse" fly (*Glossina morsitans*), but did not develop elsewhere. Bruce carried healthy horses, oxen and dogs from the mountains, where there is no nagana, to the tsetse fly country, where some became infected with tsetse fly disease. From these animals he established the fact that fly disease and nagana are the same. Bruce then brought tsetse flies up from the lowlands to the mountains, allowed them to sting animals sick with nagana, and found that for forty-eight hours thereafter the flies could infect healthy animals by stinging them. The importance of the tsetse fly as the agent transmitting nagana was emphasized by finding that the disease could not be conveyed by water, food, contact with sick animals, or other usual channels of infection. In attempting to discover where the disease arises Bruce examined the blood of the wild animals and found that many of them, although apparently in good health, are infected with the parasite of nagana; in other words, the wild animals are a permanent reservoir of infection.

Bruce also concluded that the tsetse fly acts mechanically in carrying trypanosomata, the parasite not developing while within the fly. In his experiments the trypanosoma of nagana proved fatal for most types of monkey, and for horses, mules, donkeys, cattle, dogs, cats, guinea-pigs, rabbits, rats and mice.

OTHER PROTOZOAN DISEASES

Since this discovery trypanosomata have been found to cause a number of widely prevailing diseases in the domestic animals, and experiments show that these diseases can be transferred to many other animals. Furthermore, protozoa of this type have been found widely spread in other animals, fish, etc., in which corresponding diseases have not been established. Of the diseases may be mentioned "dourine," discovered in 1896 by Rouget in African horses; "mal de caderas," discovered in South American horses by Elmassian and Voges in 1901; "Galzickte," discovered by Theiler in African cattle in 1902; and "coast trypanosis of Kamerun," discovered by Ziemann in 1902.³⁵

In a surprisingly large number of these diseases it has been established by careful experiments, reinforced by a

study of the conditions of spontaneous infection, that the parasite is carried from a sick animal and inoculated into a new victim by the bite of an insect. In the majority of trypanosomatic infections the insect is a biting fly belonging to the genus *Stomoxys* or *Tabanus* or *Glossina*.

Even after diseases caused by trypanosomata were well recognized in the lower animals the parasite was not found in man before the observation of Forde, and in his case there was at the time no proof that disease resulted from its presence. Proof was furnished, however, by Castellani, who found the same parasite in the spinal fluid drawn from a patient suffering from a fatal disease of Africa, known as "sleeping sickness," a discovery soon confirmed and extended by Dutton and Todd.

EXPERIMENTAL STUDY OF SLEEPING SICKNESS

It is impossible here to review the overwhelming amount of experimental work that has been performed in connection with sleeping sickness and trypanosomata during the last few years. Expeditions sent from England, France and Germany, and independent investigators, have been busily occupied with the subject.³⁶ As the result of investigations in this field it has already been established that trypanosomata are the cause of sleeping sickness; that the human being is infected through the bite of a fly of the tsetse fly type, *Glossina palpalis*; that the fly carries the parasite for five days or more after biting a patient or animal infected with trypanosomata, but can transmit the disease for only two days; that practically all the *Glossina* flies captured around certain lakes in dangerous districts contain trypanosomata; that the trypanosoma of sleeping sickness is fatal for some lower animals, especially for monkeys, dogs and cats, and can be transferred to them experimentally, while other animals are more highly resistant to the human trypanosoma.

In addition to the facts just stated, researches have been made to determine what changes are produced in the tissues as the result of trypanosomatic infection, and studies into the mechanism of protection and immunity are already beginning to appear.

PROBLEMS TO BE SOLVED

Many experiments have been made to discover drugs with which to combat this type of disease, with an

36. Thimm, C. A.: "Bibliography of Trypanosomiasis," London, 1909.

encouraging degree of success, and already two drugs, trypanred and atoxyl, have become recognized as having a definite value in the treatment of trypanosomatic infections. Other investigations have been made to make clear the complicated changes which trypanosomata pass through during their growth and reproduction; Schaudinn's work deserves special attention in this connection. Upward of a hundred trypanosomata have been described, which differ among themselves, either in structure or habits. It is important to determine how many species we have to deal with; to establish the specific differences; to gain information regarding the variations; so far as possible to determine the conditions under which variation occurs, and especially to obtain a clear knowledge of the manner in which these protozoa live when they are not parasitic in the blood of animals. Many experimental studies have been made which have in view some of the objects mentioned above, and among other important results already achieved a method has been devised by Novy and his colleagues for growing trypanosomata in cultures.

TRYPANOSOMATA WIDESPREAD

Enough has been said to show that diseases caused by trypanosomata are widespread and fatal for many lower animals, and that in Africa this protozoon is exceedingly dangerous to human beings. The problem of conquering these diseases is an immediately pressing problem. The interests involved are enormous, often national or even international. Success in preventing and eradicating these diseases can be hoped for only when preventive measures are based on accurate and detailed knowledge of the parasites and of the insect carriers. In attaining this knowledge it is necessary to study the sick animals, the climatic and geographical peculiarities, the distribution and habits of insects, and, above all, to study the parasites themselves. It is folly to assert that this knowledge can be gained equally well without animal experimentation. There is hardly a line of research on trypanosomata that does not require animal experimentation at one point or another. Without animal experimentation, progress in combating diseases of this group would practically cease.

CONCLUSION

It may be well, in conclusion, to try to stand to one side and view critically the experimental work that is briefly summarized in this article; to face frankly the possible charge of inhumanity and cruelty and to face equally frankly the obvious motives of the experimenters, and the results aimed at and actually accomplished. Without doubt, to one not interested in zoology and out of touch with the ideals of investigation and research, it might seem wanton cruelty to capture field mice and wild birds and to study the blood of these creatures for parasites. There might well have been no obvious connection whatsoever between such examinations and human progress. But if studies like those of Danilewsky, MacCallum and Ross had been prohibited on the ground of cruelty, it is not improbable that the ravages of malaria would be yet unchecked. The wonderful revolution brought about by the discovery that yellow fever is carried only by the mosquito was almost directly a sequel to the malaria work, and it requires no great stretch of the imagination to suppose that if animal experimentation had been forbidden the world would to-day be as powerless as ever in the fight against these two scourges.

Again, there is no question that many animals have been sacrificed in experiments connected with Texas fever, surra, nagana and similar diseases. These diseases do not even attack human beings, and, therefore, in this group of cases, we do not have to balance the value of a human life against that of an animal. The motive animating the experimenters is perfectly clear and cannot be interpreted except in one way by any one who chooses to weigh the evidence. For example, no flight of imagination could go to the point of supposing that Bruce was sent out to South Africa in order to perform brutalizing experiments, or that he would have gone for any such purpose. It is so obvious that it sounds puerile to state that Bruce's mission was to learn to master nagana and to put a stop to its ravages among live stock. The question may be raised, "Was Bruce justified in sacrificing some animals in his experiments on the chance of thereby gaining information that might be used in saving the lives, or of improving the condition of great numbers of other animals?" There can be only an affirmative answer to this question, so far as economic interests are

concerned, and even from the viewpoint of a strict opponent of animal experimentation it might seem proper to save the lives of many animals by the sacrifice of a few. The opposite attitude would, in fact, be both foolish and cruel, as it would disregard the welfare of the great majority of the animals. And yet if once it be admitted that animals may be sacrificed for the welfare of other animals the whole attack against animal experimentation collapses, for surely human progress and human welfare are objects as worthy as the welfare of the lower animals.

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MODERN ANTISEPTIC SURGERY

AND THE ROLE OF EXPERIMENT IN ITS DISCOVERY AND DEVELOPMENT

W. W. KEEN, M.D., LL.D.

PHILADELPHIA

DEFENSE OF RESEARCH PAMPHLET XII

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of the American Medical Association

"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—*Charles W. Eliot*.

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MODERN ANTISEPTIC SURGERY

**And the Role of Experiment in its Discovery and
Development**



**W. W. KEEN, M.D., LL.D.
PHILADELPHIA**



MODERN ANTISEPTIC SURGERY

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W. W. KEEN, M.D., LL.D.

PHILADELPHIA

The subject naturally divides itself into three parts: (1) the conditions before the introduction of the antiseptic method by Lister; (2) the means by which his system was discovered and developed, and (3) the conditions existing after the introduction of the method, i. e., at the present time.

My surgical life covers all three of these periods since I graduated in medicine in 1862, some years before Lister began his work. I have, therefore, fought my way from the horrors of the preantiseptic days up to the delights of the present antiseptic days.¹

I. THE PREANTISEPTIC PERIOD

In my early surgical experience every accidental wound and every surgical operation (that is, an intentional wound) was followed by inflammation and suppuration, i. e., the discharge of "pus" or "matter." This was not only constantly expected as an unavoidable process of Nature and believed to be needful for healing, but was constantly realized. Hence the pus was called "laudable" pus! How well I remember forty years ago at the beginning of each winter's session when I was the assistant of the late Professor Samuel D. Gross, his turning to the orderly and saying to him, "To-morrow, Hugh, I shall lecture on suppuration. Go over to the hospital in the morning and get a cupful of pus for my lecture." Pus, mark you, was always "on tap," so to speak, though the little hospital contained only a dozen beds!

1. In this article I use the word antiseptic as the more popular one to include also the aseptic method.

Perhaps the best way to give the reader an idea of wound conditions at that time will be to describe an ordinary operation and its results. We will suppose that it is an amputation. The surgeon approached the operation with the clean hands of a gentleman. He usually wore an old coat covered with dried blood spots from previous service. His finger-nails very likely were long and no special attention was given to them. The instruments were taken out of a velvet-lined case and were as clean as ordinary table-knives would be. The operation was done without any preliminary cleansing of the skin other than to remove any visible dirt. If the knife happened to fall on the floor it was picked up, rinsed in a basin of ordinary water and used as it was. The marine sponges then always used were washed clean in ordinary water and used over and over again even after being saturated with foul pus. The blood-vessels were tied with ordinary silk; one end was cut short, the other one hung out of the wound. After an amputation of a fleshy thigh I have often seen 25 or 30 such "ligatures," as they are called, gathered into two bundles, one at each end of the wound. The flaps were then sewed together with an ordinary needle and thread and the stump dressed first with an old rag (which, however, would be ordinarily clean) or scraped lint spread with some simple grease. Over that would be placed some other rags, lint, cotton, or other dressing, and finally a bandage. During the Civil War these greasy dressings gave place to simple cold-water dressings.

By the second day the patient would begin to have considerable fever. By the third or fourth the temperature would rise to what we now know (for medical thermometers were not in general use in that early day!) to about 103, 104 or 105 F. Then we would poultice the wound. Every few hours the patient would be disturbed, a new poultice put on to replace the old one, now cold, foul and ill-smelling, and by this time bathed with pus. I have often seen the pus escaping by the tablespoonful and the wounds alive with squirming maggots resembling chestnut worms. By this time also it was hoped that the silk ligatures, with which the arteries had been tied, had literally "rotted" loose and each one of them was gently pulled on to the discomfort of the patient. Care was taken that the ligatures with knots tied on them (in order to distinguish those that secured the large blood-vessels) should not be pulled on severely

until probably the tenth or twelfth day. Meantime the patient was tossing about the bed with pain, with thirst, without appetite, without sleep except such as morphin would secure. This at the same time dried up all the secretions, producing constipation and other evils.

By about the tenth to the fourteenth day, suppuration having been fully established and quantities of pus pouring from the wound, the fever would subside and the wound would begin slowly to heal. Of course, the healing could not be complete so long as the silk ligatures were still protruding from the wound. Sometimes they did not become detached for even months or years, but more commonly all of them would rot loose in from ten days to three weeks. When the silk ligatures on the large blood-vessels came away, if the healing process had formed in the blood-vessels a firm clot, which had become adherent, and, so to speak, "corked" it up, all went well. But, as very frequently happened, when the ligature and the rotten end of the artery were pulled off and there was no clot to act as a stopper, "secondary² hemorrhage" followed. This often came on after the patient's wound had been dressed and the surgeon had left, and, if so, very likely the first notice that the nurse had that anything was wrong would either be the gasping for breath of the patient or his moans and cries, or sometimes by the blood which had not only saturated the matress, but had even appeared in a pool on the floor. How fatal were such hemorrhages may be seen from the fact that in 2,235 cases of hemorrhage in the Civil War 61.7 per cent. of the patients died.³

I shall never forget one night about ten days after the battle of Gettysburg, when it was my business as "officer of the day" to attend to all emergency cases. That night I was called to five cases of secondary hemorrhage. To indicate what a difference there is between modern and ancient conditions, in the thirty-four years since October, 1876, when I began the practice of the antiseptic method, I have not seen as many cases of secondary hemorrhage as I treated in that one night.

It was a rare thing for any patient after such an operation to get well under three or four weeks, and it was not uncommon for healing to be delayed for three or

2. So called to distinguish it from "primary hemorrhage," i. e. the bleeding occurring at time of the accident or operation.

3. Med. and Surg. Hist. War of the Rebellion, Part 3, Surg. Vol., p. 765.

four months, so that, in spite of the great mortality, the wards of the hospitals were cumbered with convalescent patients. The rare case in which healing took place by "first intention," i. e., at once, was recounted as a triumph. To-day it is precisely the reverse. The case in which healing does *not* occur primarily and at once is regarded as a disaster.

But a prolonged convalescence was the least of the evils to which a patient was subject. A large majority of the wounds were followed by erysipelas, by lockjaw, or by blood poisoning, and hospital gangrene sometimes became a veritable plague. Gangrene in various forms during the Civil War was rife and often fatal. In 2,503 cases 1,142 patients died, a mortality of 45.6 per cent.⁴ In one variety which was frequent, hospital gangrene, a simple flesh wound scarcely larger than the bullet which made it, became larger and larger till a hand would scarcely cover it and it would eat into the tissues until one could put half his fist into the sloughing cavity.

Of 505 cases of lockjaw (tetanus), 451 were fatal, a mortality of 89.3 per cent.⁵ Pyemia or blood poisoning was terribly frequent and almost as fatal as it was frequent, for of 2,818 cases in the Civil War 2,747 patients died, or 97.4 per cent!⁶ When a joint was opened or wounded, the result was frequently either amputation or death, or not uncommonly amputation and death. Of 2,382 wounds of the knee-joint alone for which amputation was performed 1,212 patients died, a mortality of 51 per cent., and of 973 similar wounds for which amputation was not performed 591, or 61 per cent. of the patients died.⁷

Fractures, as most people know, are divided into two kinds: simple fractures in which the skin is unbroken, and compound fractures in which the broken bone protrudes through the skin. Simple fractures nearly always heal with relatively little pain and slight fever; but in the preantiseptic days when the skin was broken and the bone protruded two out of three patients with these compound fractures were sure to die.

Moreover, certain regions of the body were forbidden ground unless the surgeon were absolutely compelled to invade them. No one would open the head if he could

4. *Ibid.*, p. 824.

5. *Ibid.*, p. 819.

6. *Ibid.*, p. 858.

7. *Ibid.*, p. 367.

possibly avoid it. No one would dare to make an incision through the abdominal wall into the cavity of the abdomen unless a bullet or a dirk had gone before him and opened the way. The reason for our hesitation was that death stalked behind us.

How eloquent is the statement of Sir Samuel Wilks,⁸ that "the change came home to me in an almost startling manner from what I witnessed in the post-mortem room. Some time before [i. e., before Lister's discoveries], when reading a paper on pyemia (blood poisoning), I had no difficulty in collecting 100 cases which had occurred within a very short time previously, when suddenly this terrible malady disappeared—it was gone never to return." So, too, lockjaw (tetanus), except in accidental cuts that have been neglected and have not received proper surgical care, has almost completely disappeared. Again, at the present day one practically never sees erysipelas after operations; and in order to find illustrations of hospital gangrene to show to my classes for the last thirty years I have had to rely on pictures from the Surgical History of the Civil War and other similar sources, for I have not seen a single case in private or hospital practice since I first adopted the antiseptic method in 1876.

II. THE DISCOVERY AND DEVELOPMENT OF THE ANTISEPTIC METHOD⁹

Neither time nor space will allow me to describe the many earlier steps. Schwann, in 1837, in studying putrefaction, reached the conclusion that it was not the gases of the air, especially the oxygen, as was then universally believed, that caused putrefaction, but organic particles which floated in the air and which could be destroyed by heat. In 1854 Schröder and Dusch showed that putrefaction did not occur in organic fluids in flasks if the air entering the flasks was simply filtered through cotton wool. Pasteur, in 1864, showed that it was necessary neither to heat the air nor thus to filter it, for if the air merely entered through a tortuous tube in which the dust could settle before it reached the fluid

8. Royal Com. on Vivisection, 1907-08, Q. 7,750.

9. See Lord Lister's Collected Papers, Oxford, 1909 (later reference to these Collected Papers will be indicated simply by "Lister, vol. —, p. —"), Brit. Med. Jour., Dec. 13, 1902. The Lister number celebrating the fiftieth anniversary of his receiving his degree, and Lister's Huxley Lecture in the same journal, Oct. 6, 1900, and Cameron's "Lister and the Evolution of Wound Treatment, etc.," Glasgow, 1907.

no change took place in the fluid, or if flasks containing a material which would putrefy were left open in a place where the air had been undisturbed sufficiently long to allow the dust to settle, as, for example, in a cellar, no decomposition took place and no growth appeared in such fluids.

Lister naturally was profoundly impressed by these studies of Pasteur and he proceeded to make many experiments to confirm or disprove them. Among them I will only relate the following:¹⁰ Lister filled four glass flasks one-third full of urine and drew out the neck of each flask with a spirit lamp into a tube less than one-twelfth of an inch in diameter. Three of these long open tubes were then bent at various angles downward, while the fourth, equally narrow, was left short and vertical. Each flask was then boiled for five minutes, after which they were left with the ends of the small necks still open. Through these open mouths the air, including its oxygen, would pass out during the heat of the day and pass in during the colder night. The boiling was to kill any organisms in the liquid or on the sides of the glass. The object of the bending of the three necks downward was to allow the air to pass in and out, but to intercept the particles of dust, which, according to the germ theory, caused putrefaction. The germs, being heavier than air, could not rise in the bent necks. The fourth neck, however, being short and vertical, not only allowed the air to pass in and out, but gave a very narrow but real opportunity for dust and germs to fall into the liquid. If any of these were living organisms they could produce putrefaction. In a short time the vessel with the short and vertical neck showed growths of mold and the liquid changed its color, showing chemical changes; but in the three flasks with bent necks the urine *after four years was entirely unaltered*. A year after the commencement of the experiment a little of the urine in one of the flasks with a bent neck was poured into a wine-glass; it had not lost its original acidity and normal odor and a microscope showed not the minutest organism. In two days it was most offensive, and under the microscope already teemed with organisms. The other three flasks were subjected to a further severe and rather amusing test. Two years after the beginning of the experiment Lister

10. Lister: ii, 173; Brit. Med. Jour., 1871, ii, 225.

had to transport them from Glasgow to Edinburgh on the railway when he was appointed to the chair of surgery in Edinburgh. He took charge of these flasks himself, "nursing them carefully," as he says, "to the amusement of my fellow travelers." In the drive from the station to his house the violent rocking of the carriage churned up the contents of the flasks till the upper part was full of a frothy mixture of this proved putrescible liquid with the atmospheric gases; yet after two years more no decomposition had taken place.

The explanation of this convincing experiment was simply this: The germs in the atmosphere could not rise against gravity in any of these tubes bent downward and so could not gain access to the urine. This easily preserved a decomposable fluid for four years, although the air passed in and out freely every day. But the urine in the flask with the straight but very narrow neck in a few days had undergone decomposition. The only difference between the flasks was that the three bent tubes prevented the entrance of the germs, though not of oxygen or other constituent of the air, while the straight but equally narrow tube allowed the germs to enter through in very small quantities, and yet these few grew and produced putrefaction.

In order still further to confirm this experiment, however, Lister tested these bent tubes by the condensed beam of light which Tyndall had used and found that they were optically empty.¹¹

These experiments convinced him that it was not the oxygen or any other gas in the air that caused inflammation and suppuration, but that these were caused by *the minute organisms suspended in the air*. In dressing a wound, then, the problem was how to exclude not the air or its oxygen, which was impossible, but how to exclude the organisms in the air. This could be done by applying a dressing saturated with some material capable of destroying the life of these germs. This was the basis of the antiseptic method.¹² It must be remembered that at that time we were wholly ignorant of what now everybody knows, that there are hundreds of different kinds of germs or bacteria. Even the greatest scientists were then groping in the dark seeking for the light by observation and especially by experiment.

11. See Tyndall's charming lecture on Dust and Disease, in *Fragments of Science*, 1871, p. 275. Appleton & Co.

12. Lister : ii, 37; *Brit. Med. Jour.*, 1867, ii, 246.

About that time Lister was much struck with an account of the effect of mingling phenol (carbolic acid) with the sewage of the town of Carlisle, England.¹³ He proceeded, therefore, to experiment with it in compound fractures. I have already stated how fatal a compound fracture was in those days. Indeed, Mr. Syme, the great Edinburgh surgeon, predecessor and father-in-law of Lister, was inclined to think that, on the whole, "it would be better if in every case of compound fracture of the leg amputation were done without any attempt to save the limb." The marked success which followed his dressing these compound fractures^{13, 14} with carbolic acid led him then to experiment with its use in abscesses.^{13, 14, 15} This was followed again by such remarkable success that he was led to try it in accidental wounds and finally to intentional and extensive wounds, i. e., surgical operations.¹⁶

Practically the progressive introduction of the anti-septic system from compound fractures up to deliberate surgical operations was one vast experiment in the human living body—an experiment justified, as all the world well knows, by its splendid and continuing results. Yet when in 1880 or 1881 Lister wished to make additional experiments on animals to perfect his method still further, so stringent was the law in England that he was obliged to go to the Veterinary School at Toulouse, France.¹⁷

Like many surgeons, Lister had noticed the fact that a needle or a bit of glass would often lie for an indefinite period in the body without producing inflammation or pus, but that a bit of silk or linen thread was sure to produce pus. He believed the reason was that the thread was porous and that its interstices contained these germs which no one had then seen and identified, and that they gave rise to decomposition and produced the pus. So, Lister, from his previous experiments with phenol (carbolic acid) believed that if the thread with which an artery was tied were steeped in phenol and both the ends of the silk were cut short it might be left in the wound without producing any inflammation or

13. Lister : ii, 3 ; Lancet, 1867, i, 326, 357, 387, 507 ; ii, 95.

14. Lister, ii, 3, 32, 37 ; Brit. Med. Jour., 1867, ii, 246.

15. Lister, ii, 32, 36, 42 ; Brit. Med. Jour., 1867, ii, 246.

16. Lister, ii, 188, 199, 256, etc. ; Brit. Med. Jour., 1871, ii, 225 ; Edinburgh Med. Jour., 1871-2, xvii, 144 ; Edinburgh Med. Jour., 1875-6, xxi, 193, 481.

17. Lister, ii, 281 ; Lancet, 1881, ii, 863, 901 ; Tr. Internat. Med. Cong., London, 1881, ii, 369.

suppuration. The wound could then be closed at once—an immense gain, for it would heal at once. "Before applying these principles on the human subject," he says, "I thought it right to test them on one of the lower animals."¹⁸ Accordingly, Dec. 12, 1867, he tied the great blood-vessel in the neck of a horse, having steeped the silk for some time in a solution of phenol. Both ends were cut short, the wound was entirely sewed up and treated with phenol dressings. Ten days after the operation the dressings were removed, the wound was healed, and there was no pus! Thirty-nine days after the operation he carefully examined the artery which he had tied. The operation was a complete success, the blood current had been entirely arrested and the thread had been covered in by dense fibrous tissue. Thus encouraged, he says: "I felt justified in carrying a similar practice into human surgery."¹⁹ Jan. 29, 1868,²⁰ he saw a woman, 51 years old, with an aneurism as large as a large orange in the upper part of the left thigh. (An aneurism, I should explain, is a dilated portion of an artery, the yielding of the wall being due to disease of the wall of the blood-vessel. This dilatation continues to increase in size till finally the wall of the artery is so thin that it bursts and the patient dies from hemorrhage.) On the following day he tied the woman's artery with a piece of silk which had been steeped for two hours in phenol.

The wound was treated like that in the horse's neck, i. e., both ends of the ligature were cut short, the wound again entirely closed and a phenol dressing applied. The patient was immediately relieved of the pain she had previously experienced; she had no fever, the pulse was practically normal the entire time, and "her appetite, which had been absent during the four weeks of agony that preceded the operation, returned two days after it."²¹ She made a perfect recovery. November 30, ten months after the operation, she suddenly expired. Fortunately, Lister himself had the opportunity of making the post-mortem. He found that her death was due to the bursting of a similar aneurism inside of the chest. Examining the artery which he had tied, he found that

18. Lister, ii, 63; Lancet, 1867, ii, 668.

19. Lister, ii, 65; Lancet, 1867, ii, 668.

20. Lister, ii, 88; Lancet, 1869, i, 451.

21. Lister, ii, 89; Lancet, 1869, i, 451.

the silk had almost all disappeared, but that there was a little fluid around the remnant of the ligature, which probably would have developed into a small abscess and might have caused great mischief had she lived longer. This, therefore, suggested to him the expediency of substituting for the silk some other substance which would be more readily absorbed.²¹

In Philadelphia years before Dr. Physick had already tried animal ligatures made of buckskin, Dorsey those of kid, Hartshorn had used parchment, and Bellenger and Eve the tendon of the deer, but for various reasons these had all been abandoned. Lister determined to try catgut. Although he had great confidence in the use of catgut steeped in a solution of phenol, yet he says²² "in order to put the antiseptic animal ligature to the test, I made the following experiment," for only by experiment in an actual living body of animal or man could the question whether it was actually safe or not be surely answered. Dec. 31, 1868, he tied the right carotid artery in the neck of a healthy calf at several places with different kinds of animal ligature, including catgut. All were cut short except one end of the catgut, which was purposely left three-quarters of an inch long to determine what would become of this foreign material. The wound was completely closed and dressed. After ten days the dressings were removed and the wound found quite dry. Thirty days after the operation Lister says, on dissection, he was struck with the entire absence of any infection or inflammatory thickening in the vicinity of the blood-vessel. On exposing the artery itself he was greatly disappointed at first to find the ligature to all appearance still there and as large as ever. On more careful examination, however, he found that this apparent ligature was not the catgut ligature at all, but that this ligature had been transformed into bands of living tissue, making the artery not weaker, as silk often did, but stronger than ever at the point where it was tied. The knots had disappeared and also the three-quarters inch of catgut purposely left. Everything had been absorbed.

Even one not a surgeon can see what an enormous difference in rapidity of healing without inflammation, pain or other serious disturbance of the body this use of catgut with immediate total closure and healing of the

22. Lister, ii, 93; Lancet, 1869, i, 451.

wound provided. Before Lister, the old ligatures hanging out in bundles were always inviting infection, suppuration, erysipelas, lockjaw, blood-poisoning, hospital gangrene and death. No patient was absolutely safe till the wound was absolutely healed and this often required weeks or months. With the catgut ligature, both ends being cut short, the wound closed at once, and, the ligature being absorbed, the wound healed in less than a week, not uncommonly in three or four days, with little, if any, immediate suffering and without any ultimate danger of those many serious complications above mentioned. But no one not a surgeon can appreciate to the full the meaning of these brief words. While the patient made a smooth and speedy recovery without complications, the surgeon slept the uninterrupted sleep of the just, secure against wearing anxiety on account of sudden hemorrhage or insidious infection. The heart-breaking tragedies which often made the surgeon wish he were a hod-carrier or even in his grave are now but specters of a horrid past.

As I have said, we had no idea at first of the enormous variety and different characters of the germs. In his early studies on putrefaction, Lister spoke of them in a general way as "germs," because the various species of plants (for they are plants and not animalculæ) had not been distinguished. Now there are scores and even hundreds of known varieties. Many of these simply cause putrefaction or decomposition and are not in themselves capable of giving origin to any particular disease. Other varieties, each one of which causes a special disease and can cause no other disease, have been isolated and identified. Some of these germs cause medical diseases, with which I have nothing to do here. The germs of lockjaw, tuberculosis, anthrax (wool sorters' disease), erysipelas, glanders, etc., are among the most virulent foes with which the surgeon has to contend.

How have these been identified and how do we prevent their entrance into the system of the patient? The process is very simple to describe, but very complicated and difficult practically. Let us take the case of lockjaw for instance. A peculiar kind of germ, looking a good deal like a tack with a straight body and a large head at one end, was discovered by animal experiments by Nicolaier in earth and dust in 1884.²³ In 1889

23. Deutsch. med. Wchnschr., 1884, No. 52, p. 842.

Kitasato, the Japanese bacteriologist,²⁴ first obtained it in pure culture, former experimenters having failed because they did not know that it only grows well when oxygen is excluded.

But how do we *know* that this tack-like germ and it alone is the cause of lockjaw?

First, in a patient ill with lockjaw, this particular bacillus or germ must be discovered.

Second, a pure culture of it must be produced; that is to say, the tetanus bacillus must be separated from all other germs and cultivated by itself. Third, some of this pure culture of tetanus unmixed with any other germs whatever must be injected into an animal to see point-blank whether this particular bacillus will produce lockjaw. Fourth, from the body of this animal the same germ that was injected must be recovered. Fifth, with a pure culture of this recovered bacillus the cycle must be begun over again and completed sufficiently frequently to assure the experimenter that the connection between the disease and the germ is not accidental, but essential and invariable. Sixth, no other germ used in the same way must produce lockjaw.

In this same manner the germs that produce inflammation and suppuration, which are *the* ever-present danger to the surgeon, have been identified, and also, what is equally important, the places where they and many others exist. In this way we have determined the fact that, while there are some in the air, they are few in number and so constitute a small though a real danger. But the places where they are found and are most dangerous are on the skin and clothing of the patient, the hands of the surgeon and especially under his finger nails and at the roots of his nails, on instruments, dressings, silk, catgut, and other things used for ligatures; in fact, practically every material that one can think of. We know now how all-pervading they are. We know, too, that phenol (carbolic acid), corrosive sublimate and other chemicals, or that boiling for a certain time, or heating to a certain degree and for a certain time, will kill these germs. Thousands of such painstaking researches in test-tubes and by many other bacteriologic methods have been carried out all over the world by men either wholly unpaid, working for the love of truth and love of their fellow creatures, or paid but meager pit-

tances. Then when a discovery seems to have been made comes the needful, the finally convincing, the unavoidable experiment—in a living body itself. The only question is should Lister have made this final test first on a horse and a calf, or on two human beings? Can any one with a sane, well-balanced mind hesitate as to the answer?

III. THE RESULTS

The results of the establishment of the antiseptic method have been so extraordinary as to be incredible were it not for ample testimony the world over. They have been already stated in part, but a few words more must be added.

At present before an operation is begun the patient's skin, the surgeons' and the nurses' hands are scrupulously disinfected, sterile gloves are usually worn and every person is clothed in a disinfected gown. The instruments, dressings, ligatures, everything that is to come in contact with the wound, is carefully disinfected. Disinfected gauze "sponges" are used once and then discarded.

It is almost impossible for any one not a surgeon to understand how different are the results from this radical change of methods. No change of climate from fierce mid-winter storms to lovely summer breezes or autumn golden harvest could be greater. Most wounds now heal within a few days, one might almost say without the patient's being sick. Compound fractures and opened joints heal as if there had been no break in the skin. Arteries can be tied anywhere without fear of secondary hemorrhage. The abdomen is now fearlessly opened.

A woman with an ovarian tumor no longer has an operation postponed until it is very dangerous but inevitable, but by early operation is relieved almost without danger, even from tumors so large as to weigh twice as much as the patient herself. When I was assistant to Dr. Washington Atlee in the late sixties, before the antiseptic period, two out of three of his ovariotomy patients died, yet he was the then most famous operator in America. Now any surgeon who loses more than five out of 100 is looked at askance by his colleagues, and many, many hundreds of cases have been operated on with a mortality falling even below 1 per cent. There is not an organ in the abdomen that has not been attacked; organs which formerly when diseased could

not be touched because death was almost sure to follow are now operated on every day. In fact as I once described it, the abdominal cavity is almost the surgeon's play-ground! The stomach, the intestines, the liver, the gall bladder, the pancreas, the spleen, the kidney, every organ is operated on, and with extraordinary success. Did space permit, a more detailed statement could be given, but it could scarcely be more convincing.

In obstetrics the same happy results have followed the introduction of the antiseptic method. Puerperal or child-bed fever, which not uncommonly used to kill one-half or two-thirds or even three-fourths of the women in the maternity wards of a hospital, now is practically unknown except in the neglected cases brought into the hospital at a late date, and the preantiseptic general mortality in maternity cases has been reduced from 10 per cent. or more to 1 per cent. and less. Brain tumors, abscesses and other diseases of the brain formerly inevitably caused death, for we never dared to touch them. Now the number of recoveries is very large. Compound fractures now have a mortality of 2 or 1 per cent. or less, instead of over 60 per cent. and now very rarely require amputation; and amputations formerly followed by death in one-half the cases have a mortality of 10 per cent. or less. In general, both the soldier and the sailor are provided with the first aid packet, which contains an antiseptic dressing. This has enormously diminished the mortality of wounds received in battle.

Perhaps no better evidence of the value of the antiseptic method in civil life can be adduced than the results in three hospitals. In Munich²⁵ the General Hospital was excessively unhealthy. Blood poisoning was very frequent and hospital gangrene, which had appeared in 1872, had become annually a more and more frightful scourge until 1874, when 80 per cent. of all wounds that occurred in the hospital, whether accidental or inflicted by the surgeon, were attacked by it! At the beginning of 1875 Nussbaum introduced the antiseptic treatment. From then on till Lister's visit, presumably in the summer of 1875, *not one single case* of hospital gangrene had occurred and only one case of blood poisoning, and that a doubtful one. Erysipelas was rare and mild instead of being very prevalent and severe, and the convalescent wards, which formerly had been filled to

25. Lister, ii, 248; Brit. Med., Jour., 1875, ii, 769.

overflowing, stood practically empty. In Halle,²⁶ Volk-mann was operating in an extremely unhealthy hospital in small, overcrowded wards, with the toilet rooms opening directly into them and a large drain running directly underneath. It was so bad that it had been condemned to demolition. After his introduction of the antiseptic method in 1872, no single patient suffering from compound fracture in which conservative treatment was attained had died either from the fracture or from a necessary amputation, nor was there a single death from secondary hemorrhage or gangrene. No case of blood poisoning had occurred for a year and a half, though 60 amputations had been done. Hospital gangrene had entirely disappeared and erysipelas was extremely rare and mild.

Perhaps, however, the most extraordinary success was obtained by Lister²⁷ in his own wards in Glasgow. Lister was professor of surgery in Glasgow from March, 1865, till the autumn of 1869, but in that brief period he introduced measures that were absolutely revolutionary.. The Royal Hospital in Glasgow was overcrowded, and in some parts of the building the conditions were so frightful that the wards had to be entirely shut up for a time. Lister's own account of this is interesting. He says:

"A crisis of this kind occurred rather more than two years ago in the other male accident ward on the ground floor, separated from mine merely by a passage twelve feet broad, where the mortality became so excessive as to lead, not only to closing the ward, but to an investigation into the cause of the evil, which was presumed to be some foul drain. An excavation made with this view disclosed a state of things which seemed to explain sufficiently the unhealthiness that had so long remained a mystery. A few inches below the surface of the ground, on a level with the floors of the two lowest male accident wards, with only the basement area, four feet wide, intervening, was found the uppermost tier of a multitude of coffins, which had been placed there at the time of the cholera epidemic of 1849, the corpses having undergone so little change in the interval that the clothes they had on at the time of their hurried burial were plainly distinguishable. The wonder now was, not that these wards on the ground floor had been unhealthy, but that they had not been absolutely pestilential. Yet at the very time when this shocking disclosure was being made, I was able to state, in an address which I delivered to

26. Lister, ii, 250; Brit. Med. Jour., 1875, ii, 769.

27. Lister, ii, 124; Lancet, 1870, i, 4, 40.

the meeting of the British Medical Association in Dublin²⁸, that during the previous nine months, in which the antiseptic system had been fairly in operation in my wards, not a single case of pyemia [blood poisoning], erysipelas, or hospital gangrene had occurred in them; and this, be it remembered, not only in the presence of conditions likely to be pernicious, but at a time when the unhealthiness of other parts of the same building was attracting the serious and anxious attention of the managers. Supposing it justifiable to institute an experiment on such a subject, it would be hardly possible to devise one more conclusive.

Having discovered this monstrous evil, the managers at once did all in their power to correct it. . . . But besides having along one of its sides the place of sepulture above alluded to, one end of the building is coterminous with the old cathedral churchyard, . . . in which the system of "pit burial" of paupers has hitherto prevailed. I saw one of the pits some time since. . . . The pit, which was standing open for the reception of the next corpse, emitted a horrid stench on the removal of some loose boards from its mouth. Its walls were formed on three sides of coffins piled one upon another in four tiers, with the lateral interstices between them filled with human bones, the coffins reaching up to within a few inches of the surface of the ground. This was in a place immediately adjoining the patients' airing ground, and a few yards only from the windows of the surgical wards! And the pit which I inspected seems to have been only one of many similar receptacles, for the *Lancet* of September 25 contains a statement, copied from one of the Glasgow newspapers, that "the Dean of Guild is said to have computed that five thousand bodies were lying in pits, holding eighty each, in a state of decomposition, around the infirmary."

When to all this is added the fact that the large fever hospital was separated from the surgical hospital by only eight feet, that Lister's hospital of nearly 600 beds was cramped in area and almost always full to overflowing, and that he was operating, it might almost be said, in a charnal house, yet that those wards were continuously and conspicuously healthy and enjoyed for "three years immunity from the ordinary evils of surgical hospitals under circumstances which but for the antiseptic system were specially calculated to produce them,"²⁹ we stand convinced by such a huge unintentional experiment on man himself.

Were not results such as these sufficient to justify the experiments on animals as related by Lister himself and

28. Lister, ii, 45.

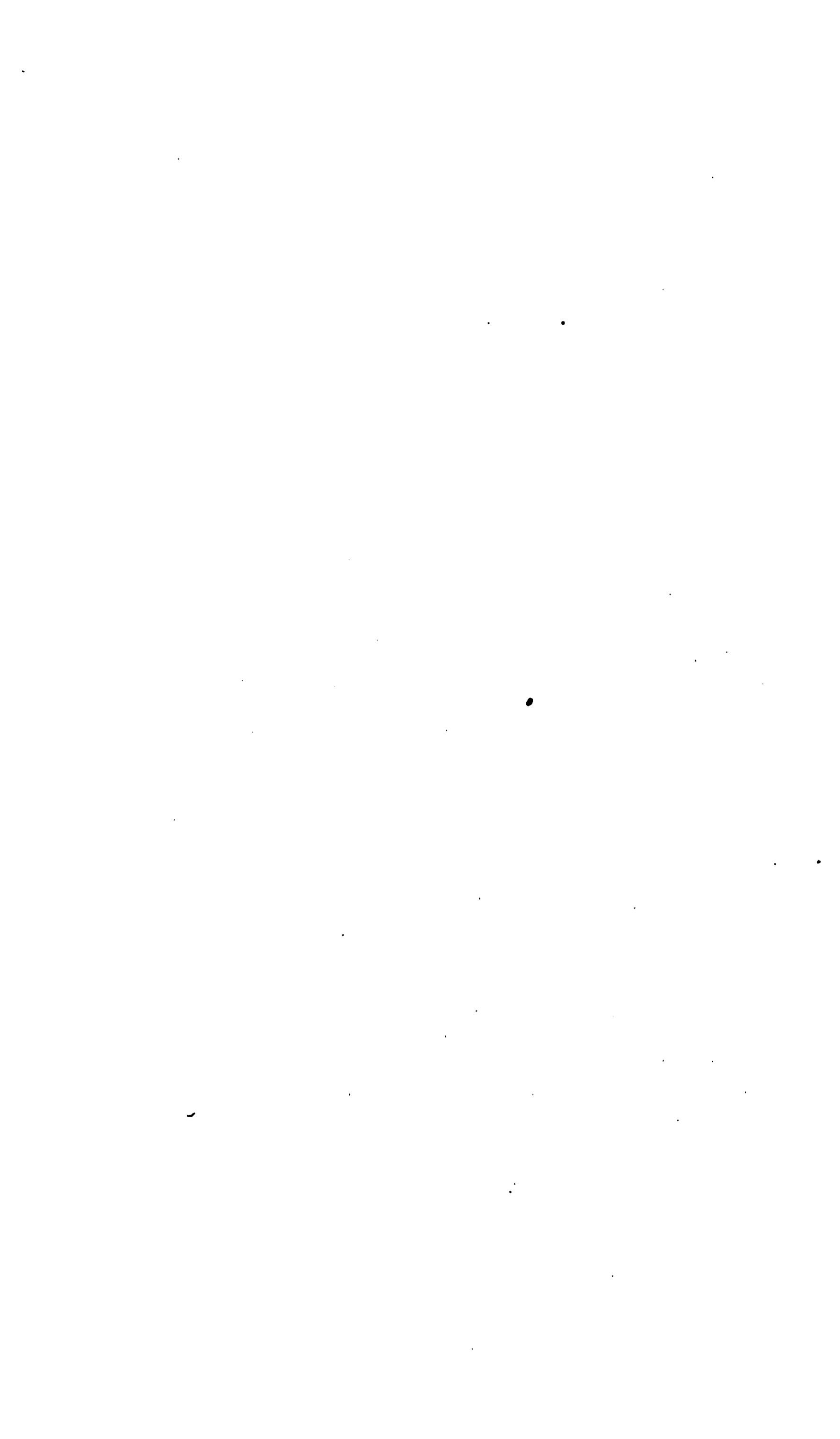
29. Lister, ii, 126; *Lancet*, 1870, i, 4, 40.

here quoted, by which such blessed relief has been brought to mankind?

What was seen in Glasgow has occurred all over the world. The surgical revolution of the last thirty years is the most momentous in the entire history of surgery. In every science—chemistry, engineering, botany, physics, electricity—the era of precise experiments has been the era when enormous and constant progress has been made. Medicine is no exception. We have closely studied disease by various observational methods, and clinical observation for two thousand years had slowly advanced our knowledge up to a certain point. Then experimental research, which employed methods of precision, varying conditions at will, noting the different results, and multiplying the experiments at will instead of waiting, it might even be years, until Nature's second experiment occurred, began its work; and in the past thirty years experimental research has produced a more fruitful harvest of good to animals and to mankind than the clinical observation during thirty preceding centuries.

But we are far from having attained perfection. In medicine and in surgery many problems of disease and death are still awaiting solution and can only be solved by the experimental method. A number of organs in the body are as yet inaccessible and others have functions of which we know little or nothing. Many operations ought to be bettered in method and in results. The cause of many diseases, such as cancer, scarlet fever, measles, whooping-cough, etc., are as yet unknown. To dispel all this ignorance and discover a cure for all these and other diseases is the earnest wish of wise and humane experimenters the world over. Shall the community aid these humane life-saving efforts, or shall they by restrictive legislation call a halt and let death slay our fellow creatures and especially our dear children? The answer is clear. It will never be other than an emphatic NO to the latter cruel course.

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Animal Experimentation in Relation to Practical Medical Knowledge of the Circulation

JOSEPH ERLANGER, M.D.
MADISON, WIS.

DEFENSE OF RESEARCH PAMPHLET XIII

Issued by the Council on Defense of Medical Research
of the American Medical Association

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and truer humanity than the humanity which would save pain or
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**J O S E P H E R L A N G E R, M.D.
MADISON, WIS.**



INTRODUCTION

There are but two paths along which the advance of medical science and art can be pressed; they are observation and experiment. The two lead to the same goal; both are beset with difficulties or even with obstacles which for the time being are, or may even forever be, insurmountable. In any case it is essential, in order to ascertain beyond peradventure that either of the paths has led us to our goal, to show that the two lead to the same place. Still, to have threaded one of the paths successfully usually assures an easy and early approach by way of the other. Indeed, the opening up of one path often leaves the finding of the other merely the matter of a single trial. When this is the case we are apt to lose sight of the fact that actually the goal has been reached by an advance pressed along both pathways.

The bearing of these remarks on the subject-matter of this paper becomes obvious when it is recalled that as subjects of observation and experiment the medical investigator employs both man and the lower animals. The method of pure observation may be employed in the study of both, whereas man can be employed as the subject of an experiment only with his full knowledge and consent and in such a way as to inflict neither bodily discomfort nor pain, except the not infrequent instances in which the experimenter himself serves as subject of the experiment. But experiments of the kind that can be made by the experimenter on himself are, for obvious reasons limited in number. There remains, then, a whole host of experiments that must be performed on the lower animals, if medical knowledge is to be advanced. This statement is true, it matters not what view we may hold as to the justifiability of experiments on animals; it is nevertheless called into question by certain misinformed or misguided persons who argue that experiments

with the lower animals cannot serve to throw any light on the functions, either normal or abnormal, of the organs of man. This objection, though untenable as it stands, contains an element of truth. It is true that inferences, based on animal experiments, as to the functions of the organs of man must be carefully guarded. When, however, they are checked by critical observation of, and painless experiment on, man, inferences from animal experiments have, we believe, led us to the greater part of our practical medical knowledge and the part which is considered the most valuable.

Scientists, then, are all agreed that the findings of the laboratory must be in full accord with the matured conclusions of bedside observation if they are to be entitled to enrolment in the category of established medical truth. Furthermore, it is equally true that bedside observation can lead to the truth only when it is checked by experiment, which in this case may, however, be made for us by the slow and precarious methods employed by Nature. It is just at this point that it becomes difficult to determine what part of medical advance along any line is due to the achievements of the animal experimenter and what part to keen observation, at the bedside, of experiments performed by disease and trauma. However this may be, all who are in a position to know are of the opinion that they are mutually helpful.

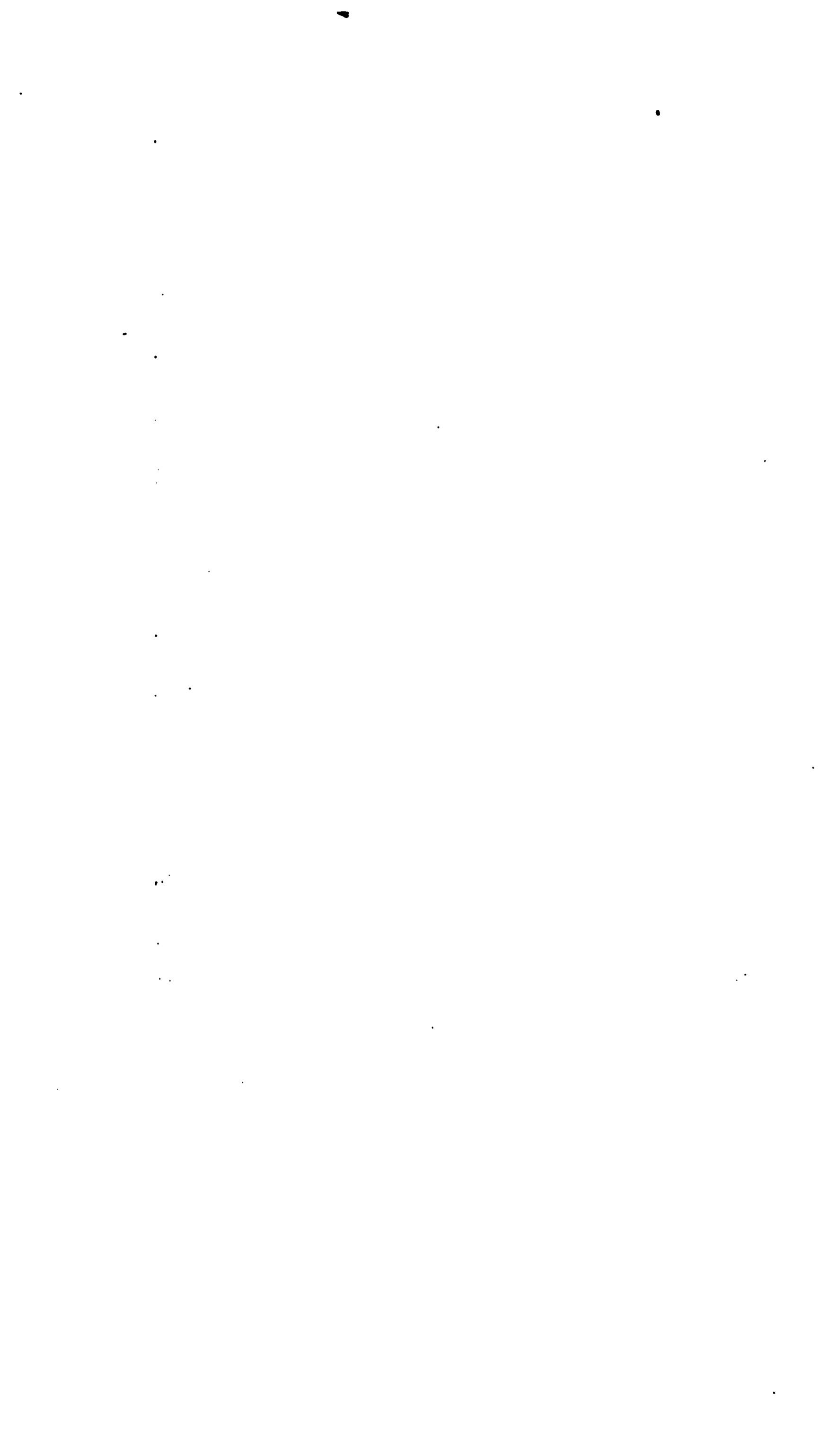
Indeed, they are mutually helpful in more ways than one. A very large part of the best clinical observation has been, and is being, made by clinicians who have had the opportunity of witnessing and performing animal experiments during their student days, or who have actually been engaged in research involving animal experimentation. The fruit of clinical observation naturally depends very largely on the attitude of mind which the clinician brings to bear on his cases. Our system of medical training recognizes this fact in requiring that the student be given every opportunity in the laboratory

to develop the critical way of contemplating things that must be employed when interrogating Nature.

It is not merely a coincidence that the periods of most rapid medical progress (Hippocratic, Alexandrian, Galenic and modern) have also been the periods of greatest activity in the pursuit of animal experimentation or its equivalent. Furthermore, it has not been merely a matter of chance that in each of these periods the most highly esteemed men (Hippocrates, Erasistratus, Galen, Harvey) were at one and the same time practitioners of medicine and animal experimenters, actually or in effect; and that at least two of them (Hippocrates and Galen) were the greatest clinicians of their times as well as the authorities of clinicians for centuries after them.

They were the authorities not alone in the particular fields in which they had conducted animal experiments, but, as a matter of fact, in every field of medicine. Is it not, therefore, permissible to assume that the relatively small number of experiments, for the performance of which they managed to snatch a few moments here and there from their clinical activities, gave to them the attitude of mind that made them the fountain-heads of all medical knowledge during the long periods of medical aridity that succeeded them?

In order, then, to give a just valuation to the debt which the physician of to-day owes to animal experimentation, account must be taken, not only of the results capable of more or less direct application to the practice of medicine, but also of such observations and experiments on man as are stimulated by experiments on animals and of the attitude of mind of the physician toward his patient determined by the scientific, and therefore critical, atmosphere surrounding his activities.



ANIMAL EXPERIMENTATION IN RELATION TO PRACTICAL MEDICAL KNOWLEDGE OF THE CIRCULATION

JOSEPH ERLANGER, M.D.

MADISON, WIS.

IN THREE PARTS

I. THE DISCOVERY OF THE CIRCULATION

The story of the discovery of the circulation of the blood has been so frequently told that it will not be necessary to review it here in any great detail. Indeed, my only reason for relating it at all is to attempt to show the part played by animal experimentation in its unfolding. The limited scope of this paper compels me to confine myself to the most important phases of, and contributions to, the subject.

The earliest recorded views on the physiology of the blood-vessel system that are entitled to serious consideration are those of Hippocrates. There seems to be no good reason for believing that Hippocrates actually performed carefully planned experiments on animals. The statement is, however, made¹ that Hippocrates (the name stands for a period rather than an individual) probably acquired his knowledge, among other ways, through observation of votive offerings, of slaughtered animals, and of injuries received in war and peace. These are tantamount to animal experiments; they are chance operations on living animals. Such slow and uncertain methods of acquiring knowledge must, however, have led to the development of a far from perfect theoretical scheme of the blood-vessel system. I call attention here only to his observation of pulsation in the aorta and pulmonary artery with the obvious comment

1. Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, Jena, 1902-5, i, 236.

that this phenomenon could have been revealed only by viewing the artery exposed in the living animal.

Whether Aristotle performed experiments on animals seems to be a matter of dispute.² In any event, however, his views are probably mainly the outcome of reflection based on dissection and the accumulated knowledge of his time. And in many respects, it might be added, Hippocrates was nearer to the truth than Aristotle.

The contribution of Praxagoras to the physiology of the blood-vessel organs consisted in drawing more clearly than had Hippocrates the distinction between the arteries and veins, and in showing that "the phenomenon of pulsation, previously regarded as a common attribute of arteries and veins, really belonged only to the arteries. . . . They were, furthermore, distinguished by the nature of their contents; for, while the veins were still considered as receptacles for blood, the arteries, according to the new view, contained no blood, nor any liquid material, but only an invisible gas or air."³

I have not succeeded in discovering the source of Praxagoras' views on the pulse; it is, however, evident that they could have arisen only from experiments or chance observation on living man or animals. His erroneous conclusions that arteries contained air must have been drawn from observations on dead, not on living animals.

The next important contributions to the physiology of the blood-vessel organs seem to have been made by Erasistratus. They were based on experiments on animals⁴ and on dissection of the human body. He seems to have been unduly influenced by the views of Praxagoras: the veins still contain nourishing blood, the arteries "vital spirits." Experimentation, however, forced him to proceed one step in advance of the views then held and admit the existence of "synanastomoses" of the arteries and veins, which, however, allowed blood to pass into the arteries only under abnormal circumstances, as in plethora and when an artery is opened.

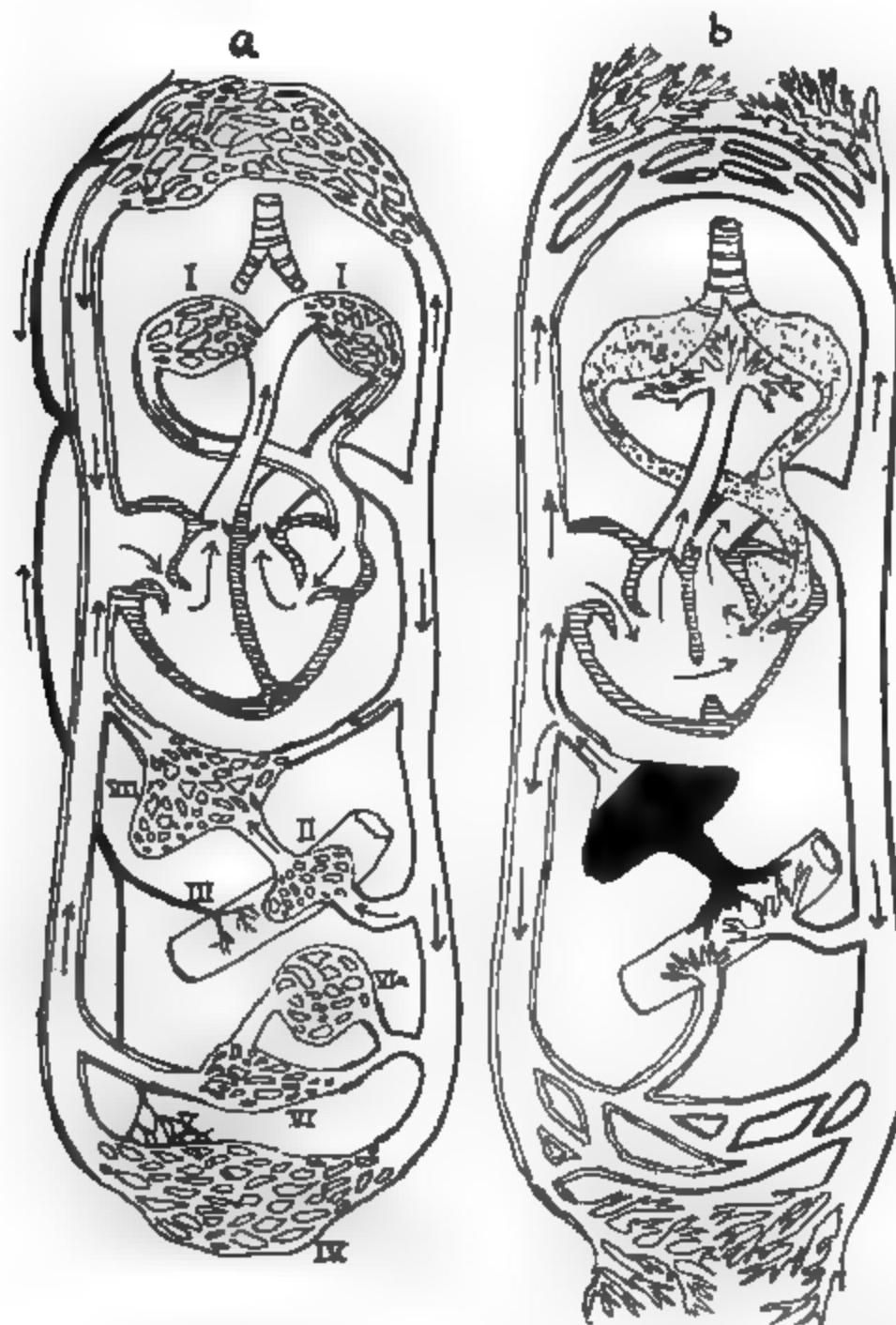
Erasistratus also describes accurately "all of the cardiac valves and their action. According to him, they

2. Nicolai: In Nagel's *Handbuch der Physiologie*, Brunswick, 1909, i, 674; and in Neuburger and Pagel Vol. i.

3. Dalton: *History of the Circulation*, p. 38.

4. Nagel: *Handbuch der Physiologie*, p. 674.

provide the mechanism by which the heart alternately takes in and expels blood on the right side and pneuma on the left."



Scheme of the circulation (Nicolai); (a) according to Harvey (modified); (b) according to Galen (reconstructed). Heart-wall shaded; arteries heavily contoured; veins doubly contoured; capillaries lightly contoured; lymphatics (nutriment) solid black; air dotted; I, lung capillaries; II, intestinal capillaries; III, chyle capillaries; IV, somatic capillaries; V, lymph spaces; VI, renal capillaries; VII, glomerular capillaries; VIII, liver capillaries.

There now occurs a gap of almost 500 years in the progress of medical science and art, and there seems to

be no evidence that careful animal experiments were made during this interval. The gap is closed by the activities of practically a single individual, Galen, through whose animal experiments, coupled with keen clinical observation, the physiology of the blood-vessel system was advanced another step.

Galen's main contribution to this subject consists of the proof that the arteries contain blood and not pneuma. Two experiments are offered as proof of this fact:

1. "Expose an artery of a living animal. Then open it by applying to it, as you choose, either the point of a writing style, a needle, a slender scalpel, or any similar instrument that will make a narrow cut. Blood will at once exude. The artery, then, must have contained blood and not pneuma."

2. "The artery of a living animal is exposed by dissection, and, after isolating it with a cord on two sides and then opening it in the middle, we showed it to be full of blood."⁶

Galen's conception of the blood-vessel system is very well illustrated in the accompanying diagrams. The nutriment taken up from the alimentary canal is converted into blood in the liver. Thence it is conveyed by the veins to all parts of the body, including the lungs (through the pulmonary artery), for the purpose of nourishing them. "The venous blood was dark, thick, and rich in the grosser elements of nutritive material." From the air carried through the pulmonary vein to the left ventricle from the lungs the vital spirits were extracted and added to the blood.⁷ Or, according to another account,⁸ the blood, traveling back and forth in the pulmonary vein, transported the pneuma from the lungs to the left ventricle. "The arterial blood (then) was thinner, warmer, bright-colored and, above all, spirituous." "As every organ is supplied with both arteries and veins, it can absorb each kind of nutriment in due proportion for its own needs." "The pulse was due to a 'pulsatile force' resident in the walls of the artery, but derived by them from the heart, in which it also existed. This was a force of active expansion, dilating the artery and attracting fluids into its cavity; while its subsequent contraction caused an expulsion of its contents in the

6. Galen : Quoted by Dalton, p. 72.

7. Dalton : History of the Circulation, p. 77.

8. Nagel : Handbuch der Physiologie, p. 675.

same degree. Thus the diastole of the artery was an active, and its systole a passive movement.”⁹

These views of the blood-vessel system prevailed until the Renaissance. At this time the dissection of the human body, which previously had been forbidden, led anatomists first to question some of the Galenic physiologic doctrines and then to seek the answers in the living animal. Thus was animal experimentation revived after a 1,200 years' sleep which began with Galen's death.

Vesalius, the father of anatomy, showed experimentally that the pulse was not dependent on the uninterrupted connection of the walls of the arteries with the heart, as Galen had maintained, since the peripheral part of a severed artery, connected with the heart by means of a cannula, still continued to beat.¹⁰

The next step was the refutation of the view handed down from the earliest times that the blood passed through the ventricular septum from the right to the left side, and the substitution in its place of the idea of the lesser circulation. Servetus, religious reformer and physician, was the first to surmise this course of the blood from the right to the left ventricle. In a book entitled “Christianismi Restitutio,” dealing almost exclusively with questions of religion, there is inserted a strikingly clear description of the pulmonary circulation. No mention is made of animal experiments, and it is usually stated¹¹ that Servetus jumped to the conclusion which Realodus Columbus subsequently proved by means of experiments on animals and probably in complete ignorance of the views of Servetus on the subject.¹² It should not be forgotten, however, that Servetus' argument was based on the then known physiology of the circulation, which was the result of animal experimentation. In his experiments Columbus “always found the arteria venalis (pulmonary vein) containing no air, but full of arterial blood and yet not pulsating.”¹³ Columbus, it might be added, was thoroughly imbued with the importance of animal experiments in the elucidation of the functions of the blood-vessel system. “One learns more in a day from the vivisection of a dog,” he

9. Dalton: History of the Circulation, p. 78.

10. Nagel: Handbuch der Physiologie, p. 677.

11. Dalton: History of the Circulation, p. 122.

12. Luciani: Lehrbuch der Physiologie, German Edition, 1905. I.

13. Dalton: History of the Circulation, p. 129.

says, "than from feeling the pulse or from reading Galen for months."¹⁴

There seems to be some difference of opinion as to whether Cæsalpinus is to be credited with making any contribution of real value to our knowledge of the blood-vessel system. Whereas, Dalton,¹⁵ on the one hand, maintains that the main purpose of Cæsalpinus was "to defend the physiologic ideas of Aristotle as against Galen, rather than to carry the doctrine of either to a further development,"¹⁶ Foster and the Italian authors,¹⁷ on the other, concede to Cæsalpinus the recognition not alone of the true action of the heart-valves and the pulmonary circulation, but also of the fact that "the flow of blood to the tissues took place by the arteries and by the arteries alone, and that the return of the blood from the tissues took place by the veins and not by the arteries." And, whereas, Borutta¹⁸ states that Cæsalpinus did not clearly understand the greater circulation—the transit of the blood from the arteries to the right heart through the veins—Luciani quotes the following experiment as showing that Cæsalpinus had thoroughly mastered the conception of the circulation of the blood: "He [Cæsalpinus] observed that if in a living animal a vein be exposed, tied and shortly thereafter cut into on the capillary side of the ligature, the first blood to exude is of a dark color, while that coming later is lighter. This observation led him to assume the existence of anastomoses between the arteries and the veins."¹⁹

In view of the difference of opinion in regard to the value of the contributions of Cæsalpinus, we may be justified in concluding that, whatever his views may have been, they could not have been clearly and consistently stated. Possibly it was for this very reason that the doctrines of Cæsalpinus made no impression on his contemporaries. It would appear that little heed "was paid to them until they were disinterred, so to speak, by antiquarian research."¹⁶

14. Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, p. 27.

15. Dalton: *History of the Circulation*, p. 147.

16. Foster: *History of Physiologie*, p. 35.

17. Luciani: *Lehrbuch der Physiologie*, 1905, i.

18. Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 332.

19. Luciani: *Lehrbuch der Physiologie*, 1905, i, 122.

How different the reception accorded Harvey's tract, "On the Motion of the Heart and Blood in Animals!" Whereas no notice had been taken of the views of Cæsalpinus in fifty-seven years, i. e., up to and after the time Harvey had committed himself in print, before sixteen years had elapsed Harvey's views had been subjected to published criticism, both favorable and unfavorable. The unfavorable criticism, it should be added, came, not from experimenters, but mainly, if not exclusively, from clinicians who, through fear that the new doctrine would wreck completely the fabric of medicine as then practiced, unwisely considered it better to bolster up the tottering structure with the old views than to rebuild it on the firmer foundation of animal experimentation. Those who then and since have put Harvey's views to the test of experiment have succeeded in substantiating him in all but a few minor details. The reason for the stability of Harvey's views may be gleaned from the well-known introductory words to the tract which laid the foundation of modern experimental medicine:

When I first gave my mind to vivisections, as a means of discovering the motions and uses of the heart, and sought to discover these from actual inspection, and not from the writings of others, I found the task so truly arduous, so full of difficulties, that I was almost tempted to think with Fracastorius, that the motion of the heart was only to be comprehended by God. . . . At length, and by using greater and daily diligence and investigation, making frequent inspection of many and various animals, and collating numerous observations, I thought that I had attained to the truth, that I should extricate myself and escape from this labyrinth, and that I had discovered what I so much desired, both the motion and the use of the heart and arteries. From that time I have not hesitated to expose my views on these subjects.²⁰

With the appearance of Harvey's work, the blood-vessel system, with at best imperfectly understood functions, becomes known to the world as the circulatory system, a term that stands at one and the same time for a system of organs and the mechanism thereof.

Harvey's demonstration of the circulation of the blood was incomplete; he had to assume the existence of "porosities of the flesh" in order to account for the passage of the blood from the arteries to the veins. Four years after Harvey's death, however (1661), the

20. Harvey: *De Motu Cordis*, 1628; transl. by Willis.

missing link was supplied by Malpighi, at one and the same time physician, anatomist, physiologist, histologist and the founder of scientific pathology. With the aid of the microscope, Malpighi succeeded in following in the lung of the living frog the course of the blood from the arteries through the capillaries into the veins, "so that," to use Malpighi's words, "the circulation of the blood is evidently exhibited."²¹

Thus, in barest outline, was the fundamental action of the blood-vascular system determined. The necessary facts, it has been seen, were gathered from all sources; the most important and decisive ones, however, were all the outcome of experiments on animals. Inferences from structure were made by all investigators; but, unsupported by experiment, they failed, even in the hands of Harvey, to lead to the truth. Nor could the case have been otherwise; a new mechanism, to be understood, must be seen and studied while in action.

The discovery and demonstration of the circulation of the blood ends the first phase of the physiology of the blood-vascular system and begins the second. With this second phase the physiologists of to-day are still concerned; it has to do with the elaboration of the details of the circulation. The limits of this paper make it impossible even to enumerate the lines along which the investigations have been carried, were the list to include only those of direct practical significance, and those in which animal experimentation has played a part. For the purpose of recalling to the mind of the reader some of the more important results of this activity, mention may, however, be made of the discovery of the automatic action of the heart, its regulation through the inhibitory and acceleratory nerves, of the vasomotor mechanism; of the measurement of the blood-pressure and blood-velocity, of the origin and transmission of the pulse as a wave, of the cause of the heart sounds, of the survival of organs with artificially maintained circulation, etc. Reference will be made in Parts II and III of this paper to the practical bearings of these and of many other contributions.²²

21. Dalton: History of the Circulation, p. 224.

22. It will be quite impossible to give full credit to all investigators in the fields referred to. Nor am I sanguine enough to believe that I have succeeded in my attempt to mention the first workers who have called the attention of the scientific and medical world to the subjects to be discussed.

II. MODERN VIEWS OF AND METHODS OF STUDYING DISEASES OF THE CIRCULATION

In Part I of this paper the attempt has been made to present in the briefest possible form the fact that we owe our knowledge of the circulation primarily to animal experimentation. This paper has been written for the purpose of showing the practical bearings of the knowledge so gained on our understanding of certain phases of human pathology.

There could be no more emphatic way of bringing home to the practicing physician the practical results, so far as the cardiovascular system is concerned, that have accrued through the application to human pathology of the results of experiments on animals than to transcribe in full for his consideration the parts dealing with disease of the blood-vessel system, first, from some work that was standard before the Renaissance, i. e., before the importance of animal experimentation was fully realized, and, secondly, from a work that is standard to-day, calling attention to the differences between them and indicating how far such differences are due more or less directly to experiments on animals. Unfortunately, however, the limited scope of this paper precludes the full treatment of the subject in this way. I must, therefore, content myself for the present with brief extracts and discussions which, it is hoped, will furnish the reader material about which he may group his own ideas on the subject. It should be added that the extracts given below have not been selected at random, but only after careful consideration and as representing the views which, in my opinion, are in closest accord with those of the most enlightened thought of the time.

I select as the work from which to quote the views held prior to the revival of learning, "The Seven Books of Paulus Ægineta with a Commentary Embracing a Complete View of the Knowledge Possessed by the Greeks, Romans, and Arabians on all Subjects Connected with Medicine and Surgery,"¹ which dates from the seventh century. This work has been selected, first, because of its accessibility, and, secondly, because it

1. Transl. by Adams, London, 1844.

purports to be a more or less complete compendium of the then known medicine.

The section on the heart is brief and may be quoted practically without abbreviation:

When the heart itself is primarily affected, the case is far beyond all medical aid, occasioning sudden death; and also in the inflammations and erysipelas of it, strong distempers in very acute fevers, and hemorrhages when it is wounded, especially in the left ventricle. When it is affected sympathetically with the brain, the liver, the orifice of the stomach, and from sorrow, fear, and many other causes, it brings on the affection called syncope, being a sudden collapse of the vital powers, indicated by prostration of strength, delinquum animi, a small pulse, coldness of the extremities and copious perspiration. When this affection is of a violent nature, it also is irremediable; but if the strength stands out, it may sometimes be relieved. But strong palpitations of the heart often arise from a fulness or effervescence of its blood. When, therefore, the heart is overheated, it renders the respiration large and dense, but when it is too cold, the respiration is small and rare. The complete cure of syncope of the heart, when it occurs among the symptoms of fever, we have treated in the Second Book. This only may be added, that when collapse gains ground after friction and ointments have been applied to the extremities, and after purification of the floor, and other cooling means, we must sprinkle on the parts of the body which are sweating powdered myrtle, limolian earth, or amber, or pomegranate-rind with marena, or Samian earth with gum; and cataplasms of mustard or pellitory, adarce, are to be applied to the cold extremities, as far as to the groins and arm-pits. The food should be bread out of water, or out of cold diluted wine, swine's feet and joints and snout, and fowls; all things to be given in a cold state. . . .?

Under the topic of "palpitation of the heart" there is found the following interesting passage:

"I knew a certain person," says Galen, "who suffered an attack of palpitation of the heart every year in the season of spring. Wherefore, having for three years experienced benefit from venesection, in the fourth he anticipated the attack by getting bled, and so escaped from it, and did so for many years afterwards, using at the same time a suitable diet. And yet even he died before attaining old age, as every other person in this complaint does, some being suddenly cut off in acute fevers by syncope; but some of them without syncope, being unexpectedly deprived of life, as if by apoplexy. The majority of those who are thus affected do not reach the fiftieth year of age, but pass the fortieth."

Finally the ideas held by Paul of Aegina in regard to dropsy are set forth in the following passage:

Where the liver is greatly congealed, sometimes primarily, as when it has been inflamed, indurated, or otherwise affected, or when from sympathy with other parts the process of sanguification ceases, and the affection is called dropsy. . . . But, for the most part, it arises from hardness and scirrhus about the spleen and liver, and from chronic deflexions about the intestines; whereby it happens that the belly is swelled, while the rest of the body is melted owing to its not being nourished. . . . Sometimes throughout the whole body a colder and more pituitous blood is collected, either coming from the liver, or deriving its origin from a melting down of the flesh of the whole body, which is as it were converted into water. . . . In treating these complaints, we commence generally with evacuation; but in ascites and tympanites it is by administering hydragogue medicine; and in anasarca by blood-letting. . . . When those who have ascites are not benefited by any of the remedies already described, we must have recourse to paracentesis, which does not apply to any of the other varieties of dropsy.³

The quotations cited above show that the theory and practice of the time of Paul of Aegina, which are not to be scoffed at, are based on the physiology of Galen, who, by some, is considered the founder of physiologic experiments, carefully planned and executed.⁴ It will do no harm to call attention again to the fact that the first careful experimenter, and the last to experiment prior to the Renaissance, was the authority of all practitioners through the long period of the dark and middle ages. And, it may be added, that so far as Galen's followers expounded views that were the result of experiments on animals, just so far were they indebted to animal experimentation for their clinical knowledge. It would carry me too far afield to attempt a detailed exposition of this dependence.

Nor is the modern practitioner any less dependent on the results of animal experimentation than were his predecessors.

The problem for a physician to solve when confronted with a case of circulatory disease is, which of the many factors in the maintenance of the circulation are at fault? . . . The factors in the normal maintenance of the circulation are: an efficient myocardium with a sound directing innervation,

3. Paul of Aegina: Seven Books . . . , i, 569.

4. Neuburger and Pagel: Handbuch der Geschichte de Medizin, 1, 572.

efficient and unobstructing valves at the atrioventricular and arterial orifices, an aorta and branches of suitable caliber with elastic walls.⁵

The part that animal experimentation has played in determining this problem may be made clear by paraphrasing it to suit our purposes, thus: The animal experiments of Harvey, Malpighi and others have demonstrated that in animals the blood is propelled through the blood-vessels in a circle through the pump-like action of the heart, whose active tissue consists of muscle (experiments of Harvey,⁶ Stenson⁷ and Borelli⁸), not of parenchyma.⁹ Clinical experience, viewed in the light of Harvey's experiments, has shown that in man, too, the blood circulates. In disease of the cardiovascular system the circulatory mechanism does not work properly. What is at fault? It may be Harvey's force-pump, not the (mainly) suction-pump of the earlier writers. The pump may fail to work efficiently through unfavorable action of the nerves which regulate its movements. That the nerves of the heart do not determine its action was demonstrated by the experiments of Haller¹⁰ (1757); that the work of the automatic heart is regulated by its nerves was demonstrated by the experiments of the Weber brothers¹¹ (1845), who discovered the tonic action of the vagus mechanism, and by von Betzold¹² and Cyon,¹² who determined through animal experimentation the action of the accelerator nerve. The contracting myocardium can move the blood in a circle only through the medium of the valves of the heart. It is obvious that any one familiar with the structure of the valves could easily infer their mechanical action, provided the information was at hand as to whether the heart acted after the fashion of a force-pump or a suction-pump or both. Erasistratus seems to have been familiar with the action of the valves, but, swayed as he was by the belief that the heart alternately took in and expelled materials, his knowledge served neither his contemporaries nor his successors any

5. Hoover: In Osler's Modern Medicine.

6. Harvey: *De Motu Cordis*.

7. Stenson: *De Musculis . . .*, 1664. Quoted in Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 343.

8. Borelli: *De Motu Animalium*, 1681. Quoted in Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 344.

9. See Ozanam: *La circulation et le pouls*, Paris, 1886, p. 75.

10. Quoted by Howell: *Text-Book of Physiology*, 1905, p. 496.

11. Quoted by Howell: *Text-Book of Physiology*, 1905, p. 513.

12. See Richet's *Dictionnaire de Physiologie*, 1900, p. 103.

useful purpose. After Harvey had, however, demonstrated the true action of the heart and after this action had been more convincingly demonstrated by the animal experiments of Marey¹³ and others, further experiments were needed only for the purpose of working out the finer details of the valvular mechanisms. The need of "efficient and unobstructing valves" became obvious. The mechanical advantages of elastic tubing in the maintenance of the circulation were pointed out by the animal experimenter, Borelli,¹⁴ and the whole question was studied in greater detail by S. H. Weber¹⁵ (1850).

All of the factors in the maintenance of the circulation, then, which a modern clinician considers of prime importance have been brought to light directly or indirectly through animal experiments:

Pre-Harveian treatises on diseases of the blood-vessel system, therefore, differ from modern works on the same subject in at least two fundamental respects: 1. The foundation of the latter consists of a clear conception of the function of the parts concerned, this conception being based for the most part on demonstrated facts. 2. It is recognized in modern treatises that disease is due to disturbed function.

It is interesting to trace in somewhat greater detail the effect that the discovery of the circulation of the blood and the consequent renewed activity in experimental physiology had on the discovery of diseases of the heart. It has been shown that before the time of Harvey diseases of the blood-vessel system received very scant mention in the standard texts. Excepting treatises on the pulse and on bleeding, the writings on the subject were very scant indeed, while but very few distinct diseases were recognized. Of diseases of the heart and symptoms, mention is made in pre-Harveian literature only of hydrops pericardii, syncope, palpitation, erysipelas, abscess, tumors and wounds, the mythical *cor hirsutum*, and, late in the sixteenth century, dilatation, and these conditions were very imperfectly understood.

On the other hand, within the hundred years whose beginning is marked by the publication of Harvey's tract (1628) distinct progress toward the modern conception of cardiovascular disease can be discerned. Har-

13. Trav. du laboratoire de Marey, 1877, iii.

14. Borelli: De Motu Animalium, 1681. Quoted by Neuburger and Pagel: Handbuch der Geschichte der Medizin, ii, 336.

15. Abstr. in Luciani: Lehrbuch der Physiologie, i, 191.

vey himself describes a case of rupture of the left ventricle, and a case of *cor bovinum* with dilatation of the aorta, together with the symptoms during life. Lower, one of a trio of brilliant animal experimenters of Harvey's time, discusses hydropericardium as a result of venous stasis, and also a case of adhesive pericarditis.¹⁶ Cooper described aortic insufficiency and appreciated its significance.¹⁷ The same lesion as well as stenosis of the mitral orifice, with an ingenious explanation of the pulse quality in that disease, as well as many other interesting references to cardiac disease encountered in the course of his practice, are mentioned by Vieussens in a work devoted primarily to the normal structure and functions of the heart.¹⁸ Finally, in a work on the movement of the heart and on aneurisms, Lancisi makes many important contributions to cardiac pathology and pathologic physiology.¹⁹ Besides making many other valuable additions to our knowledge, he ascribes sudden death to structural defects, mechanical obstructions and nervous diseases of the heart. He is the first to call attention clearly to the significance of engorgement of the veins of the neck in dilatation of the right cavities of the heart, a diagnostic sign of great importance which could not have been comprehended had Lancisi had at his disposal only the ancient view that the veins and the blood originate in the liver. In this connection he speaks of tricuspid insufficiency. He also understood almost perfectly the symptoms of dilatation of the heart and their cause.

The most important of the early works on diseases of the heart appeared, however, something over a century later than Harvey's great contribution. This is Senac's "Treatise on the Structure of the Heart, on its Action and its Diseases" (Paris, 1749). Perhaps the most striking feature of this work is its modernness. There is no difficulty in comprehending the conditions described by the author; so modern are the thoughts that the reader can hardly believe that he has before

16. Lower, Richard: *Tractatus de Corde*, 1669. Quoted by Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 634.

17. Cooper: *Phil. Tr.*, London, 1705, No. 299. Quoted by Gibson: in Osler's *Modern Medicine*.

18. Vieussens: *Traité nouveau de la structure et des causes des mouvements naturels du cœur*, 1715.

19. Lancisi: *De Motu Cordis et de Aneurysmatibus*, Rome, 1728. Quoted by Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 635; and Rosenstein: in Ziemssen's *Handbuch*, Ed. 2, 1879, vi.

him a work written over one and one-half centuries ago. I am of the opinion that Senac's pre-eminence in the field of cardiac pathology must be attributed largely to his grasp of the anatomy and physiology of the heart. However this may be, it is not without significance that of the two large volumes Senac has written on this subject about one and one-half are devoted to an exposition of the anatomy and physiology of the circulation.

Of his many important contributions, space will permit of reference to but one. To Senac must be attributed the recognition of the venous pulse as a diagnostic sign. At the same time he recognizes the most important factor in its production. Speaking of dilatation of the right auricle, he says (p. 411): "It is evident that dilatation of the vena cava should be no less frequent; the blood is pushed with force when contraction diminishes the cavity, and this is the cause of a singular phenomenon; the jugular veins beat with regularity. . . ." Whether Senac was here dealing with the pulse produced by a hypertrophied right auricle or by regurgitation through the tricuspid orifice cannot be determined.

From our standpoint, however, it matters little, since in either case the phenomenon, without a knowledge of the "motion of the heart," would have been without significance as a diagnostic sign.

At about the same time Morgagni,²⁰ the father of pathologic anatomy, called particular attention to the mechanism of the circulatory disturbances caused by valvular lesions and explained the symptom of cyanosis as a congestion of blood.

DEVELOPMENT OF CLINICAL METHODS

Through animal experimentation coupled with inferences from anatomy, the circulation of the blood in animals was demonstrated. Observations on human beings sufficed to show that the results of animal experiments were applicable to man without change. And finally clinical conditions were gradually recognized in the light of normal function and a more logical classification of disease became possible. Except, however, the relation between right-sided lesions and venous engorgement and

20. Morgagni: *De Sedibus et Causis Morborum, Ven.*, 1761. Quoted by Ziemssen: *Handbuch der speciellen Pathologie, etc., Ed. 2*, 1879, iv.

pulsation, exact methods of recognizing pathologic conditions in living man were, aside from the evident symptoms exhibited by the patient, almost entirely lacking. It is to the relation which the development of these methods bears to animal experimentation that attention will next be directed.

At the outset it should be made clear that the problem of developing methods must, from the nature of the case, be largely clinical, since what are desired are methods for the detection of conditions which are commonly seen in man, and rarely in animals, and which may be studied in animals usually only after the diseased condition as disclosed in man has been reproduced in animals.

The methods now employed by the physician in his effort to detect deranged function of the organs of the circulation are usually classified under the heads of inspection, palpation, percussion and auscultation. Three of these principles, namely, inspection, palpation and auscultation, are as old as the seeing eye, the feeling hand and the hearing ear. Their origin, therefore, bears no relation to animal experiments. The same statement is not, however, true of their subsequent development and elaboration. The eye must be trained to see and the hand to feel. Few of us are gifted with the power of seeing or feeling what others before us have failed to see or feel. Yet the eye or hand when provided with a working hypothesis or a demonstrated fact can often discover or discern phenomena which otherwise might have escaped them entirely. For instance, Galen, than whom the world has had no keener observer, must frequently have watched the beating heart exposed in animals—he actually records having seen the beating heart of man, exposed by disease—yet he failed to recognize what Harvey discovered in the same way, but probably with his working hypothesis more or less fully developed, namely, that the active phase of the heart's motion, and the phase corresponding with the pulse in the arteries, is its systole and not its diastole. To the student of to-day, guided, as he is, by demonstrated fact, it is almost inconceivable that any one could for a moment have held any but our present view in regard to the motion of the heart.

Inspection

And so it is that to-day pallor, cyanosis, dyspnea, pulsation in the veins and arteries, as well as many other visible signs of disease are quickly recognized even by the beginner and their significance almost as quickly grasped.

Whereas pallor now, and as was probably the case even at the time of Hippocrates, denotes bloodlessness, we of to-day have learned to distinguish between pallor of several different origins; for example, the pallor of anemia, of deficient heart action (of nervous origin),²¹ of deficient vasomotor tone in the splanchnic area,²² the two latter conceptions arising out of animal experiments, and the pallor of localized vasomotor overaction,²³ likewise a conception which the clinician owes to physiologic experiments. The ability to distinguish these and other types of pallor is not merely an accomplishment devoid of all practicality; rather it is through this ability that the practitioner is placed in a position to discover causes and to remove them by means of rational treatment directed specifically to them and, if it is so desired, to nothing else.

To be somewhat more specific, I shall quote for purposes of illustration a passage from Paul of Aëgina. Under the title of "Deliquium Animi or Swooning" (one of the topics treated under "Fevers") this author says:²⁴

Several strong ligatures are likewise to be applied; when the evacuations are downward, to the arms, and, when upward, to the legs. The patients are also to be placed in an easy erect posture, and a cupping instrument applied, so as to produce revulsion to the opposite part of the body. . . .

It is quite unnecessary to call the attention of the reader to the points at which the above (which probably is largely Galen's) treatment is at variance with ours, which is dependent on modern conceptions, both mechanical (Spallanzani²⁵ (1729), Haller,²⁶ and others) and vasomotor (Bernard²³ and others) of the circulation.

21. Goltz: Virchows Arch. f. path. Anat., 1863, xxvi, 11.

22. Ludwig and Cyon, 1866. Quoted by Luciani: Lehrbuch der Physiologie, i, 281.

23. Bernard and Brown-Séquard, 1851-2; Quoted in Schäfer's Text-Book of Physiology, 1900, ii, 131.

24. Paul of Aëgina: Seven Books . . . , i, 327.

25. Quoted by Ozanam: La circulation et le pouls, p. 110.

26. Quoted by Neuburger and Pagel: Handbuch der Geschichte der Medizin, ii, 351.

Cyanosis, too, has always been recognized ; but how, in the absence of facts brought to light by animal experimentation, could the distinction be made between the cyanosis of acquired heart disease, where it always is an indication of back-pressure into the veins from a congested right heart,²⁰ the cyanosis of insufficiently aerated blood (Lower, Mayow and Guericke, Lavoisier and others²⁷) and the cyanosis of local asphyxia, probably of vasomotor origin (Bernard,²³ Thompson²⁸ and others).

Dyspnea as a symptom of cardiovascular disease is occasionally hinted at by the early writers. Thus, Paul of Aegina says: "When the heart is overheated it renders the respiration large and dense, but when it is too cold the respiration is small and rare."²⁹ This relation between the heart and the respiration was probably suggested by the Galenic doctrine that the main functions of respiration were to remove from the body the fuliginous vapors and to cool the blood which is warmed by the innate heat of the heart. That there is an element of truth in this doctrine cannot be denied (and we should not lose sight of the fact that this, in large part, is the fruit of animal experiments), yet it is evident that such a view would have been entirely inadequate to bring to light the true clinical significance of cardiac dyspnea. Deficient internal respiration due to slowing of the blood-stream (a sequel to the demonstration of the circulation) and engorgement of the lungs, on which depends also the hemoptysis of heart disease (Albertini³⁰), now account quite satisfactorily for this condition and suggest lines of treatment.

Palpation

The way in which the animal experimenter has helped our hands to feel for clinical states also may be illustrated by a few examples.

From time immemorial the pulse has been held to have great diagnostic value. Indeed, until quite recently and even now in some parts of the world, China, for instance, a great deal more significance was or is attributed to the pulse than is justified by experiment. The

27. Neuburger and Pagel : *Handbuch der Geschichte der Medizin*, ii, 341 et seq.

28. Thompson : *Jour. Physiol.*, 1894, xvii, 120.

29. Paul of Aegina : *Seven Books* . . . , i, 501.

30. Neuburger and Pagel : *Handbuch der Geschichte der Medizin*, ii, 636.

result was that classification of the pulse was carried to a degree of refinement that is bewildering. Thus, Sancto-rius, in 1625, recognizes seventy-three significant kinds of pulse.³¹ His time probably marks the pinnacle of pulse analysis. With the advent of careful experimental methods, as laid down by Harvey, and largely through the efforts of experimentalists, the Weber brothers³² in particular, and down even to the present day³³ the number of significant varieties of pulse has constantly diminished. And, what is of far greater interest, the significance of the few varieties now recognized has become far more definite. The first step toward this simplification was made by Harvey when he recognized the right relation between the contraction of the heart and the pulse in the arteries. Paul of Ægina thus explains the Galenic view of the pulse:

The pulse, is a movement of the heart and arteries, taking place by a diastole and systole. Its object is twofold; for by the diastole, which is, as it were, an unfolding and expansion of the artery, the cold air enters, ventilating and resuscitating the animal vigor . . . ; and by the systole, which is, as it were, a falling down and contraction of the circumference of the artery towards the center, the evacuation of the fuliginous superfluities is effected. . . . They (the arteries) arise from the heart, and are distributed to all parts of the body, and, therefore, all the arteries pulsate in a similar manner and like the heart, so that from one of them you may judge concerning all the rest.³⁴

The fact that "all the arteries pulsate in a similar manner and like the heart" is the very foundation of the diagnostic significance of the pulse. Naturally, however, the errors in the Galenic conception dragged into medicine along with them many misconceptions with regard to the mechanism of the pulse, and consequently led the physician to feel events which actually do not transpire. For instance, we find that, in accord with the idea that the pulse consists of an active systole and an even more active diastole of the artery itself, the Galenists divided the time of rest between pulses into the diastolic rest and the systolic rest. With the adoption of the views on the pulse as determined by Harvey, by the Weber brothers, animal experimenters, and with the invention of the first

31. Quoted by Ozanam: *La circulation et le pouls*, p. 49.

32. Quoted by Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, ii, 373.

33. Frank: *Ztschr. f. Biol.*, 1905, xlvi, 441.

34. Paul of Ægina: *Seven Books* , i, 202.

practical sphygmograph by animal experimenters (Vierordt³⁵ and Marey) the clinicians came into the right conception as to the form and time relations of the pulse: the distinction made by the Galenists, which we now know to be without foundation in fact, is no longer taught. The chief value of the sphygmograph, it should here be added, does not consist in the means it affords us of making for purposes of study a graphic record of the pulse, although this result is not to be undervalued; rather it is that the knowledge of the true form of the pulse-wave as determined with the sphygmograph makes it possible for the student to discern more easily and to value by simple palpation what otherwise he might never, or only after diligent application, learn to discover.

It may reasonably be doubted whether the Galenists had any clear ideas in regard to pressure and pressure variations in the arteries and veins. It is true that in their classification of pulses they speak of the "consistence of the body of the artery"³⁶ and distinguish three varieties thereof, namely, hard, soft and moderate; yet it cannot be made out from the context whether "consistence" is a property of the arterial wall proper or one imparted to it through the pressure of the blood in the lumen. However this may be, we owe to the Rev. Stephen Hales³⁷ the demonstration, by means of his classical experiments on animals, of the pressure in the arteries and veins and some of their variations. These experiments, multiplied and analyzed by subsequent investigations (Ludwig,³⁸ Marey³⁹ and others), gave to the practitioner a new clinical idea, that of attempting to determine by palpation the degree of arterial tension and to correlate tension with the clinical picture as a whole.

It was Traube who introduced the term "tension of the arterial wall" into the clinic. He had so often felt of the exposed artery of animals and had so often compared this with the pressure as measured by a manometer connected with the artery that he was in a position to estimate through palpation alone the pressures in man.⁴⁰ But Traube's method of training the touch is

35. Vierordt: *Die Lehre vom Arterienpuls in gesunden und kranken Zuständen*, Brunswick, 1855.

36. Paul of Aëgina: *Seven Books* . . . , i, 202, et seq.

37. Hales, Stephen: *Statistical Essays*, 1733.

38. Ludwig: *Arch. f. Physiol.*, 1847, p. 243.

39. Chauveau and Marey: *Mém. Acad. de med.*, 1863, **xxvi**, 302.

40. Quoted by von Basch: *Berl. klin. Wchnschr.*, 1887, **xxiv**, 179.

not a practical one for general use. Furthermore, palpation of pulse tension, like palpation of pulse form, had to be controlled and taught with the aid of some instrument of greater precision than the finger. The sphygmomanometer, the first practical form of which was devised by an animal experimenter and clinician (von Basch⁴¹), and which has been tested by animal experiments, was the result of this need. With this instrument Cushing,⁴² guided by experiments performed on animals, discovered not only a sign of intracranial hemorrhage, but also a signal for operative interference in that condition. Most of the work in this field, however, is so recent that it is hardly necessary to refer specifically to other practical results that have come of it in the diagnosis, prognosis and treatment⁴³ of cardiovascular disease. I cannot refrain, however, from making a brief reference to a recent report by Williamson showing the prognostic value of blood-pressure estimations. Of seventeen patients with a blood-pressure over 200 mm. Hg. (the normal is about 120) Williamson was able to keep track of thirteen. Of these, eight had died within from two to three years.⁴⁴

Neither inspection nor digital palpation sufficed for the correct analysis of the venous pulse. This was not possible until we had at hand the results of animal experiments (Riegel⁴⁵ Frédéricq,⁴⁶ Porter⁴⁷ and others) and until such results had been applied practically in the analysis of the human venous pulse (Riegel,⁴⁵ Mackenzie,⁴⁸ and others) through the use of graphic methods primarily developed by animal experimenters (Ludwig, Marey and others). This whole subject is so new that it is quite unnecessary to remind the clinician of the practical results in the diagnosis of cardiac disease that have accrued therefrom.

Percussion

The direct object of percussion is anatomic rather than physiologic; it seeks to determine the limits of organs and the nature of their contents. Its indirect

41. Von Basch : Ztschr. f. klin. Med., 1880, ii, 79.

42. Cushing : Am. Jour. Med. Sc., 1903, cxxv, 1017.

43. Oliver : Treatment of High Blood-Pressure, Med. Press and Circular, Feb. 2, 1910.

44. Williamson : Clin. Jour., June 30, 1909.

45. Riegel : Deutsch. Arch. f. klin. Med., 1882, xxxi, 1, 471.

46. Frédéricq : Trav. du laboratoire de Liège, 1890, iii, 85.

47. Porter : Jour. Physiol., 1892, xiii, 513.

48. Mackenzie : Brit. Med. Jour., March and April, 1905.

object, however, is to discover disturbed function. It therefore follows that the intelligent interpretation of the secrets brought to light by percussion can be made only by one who is familiar with the physiology, normal and pathologic, of the organs of the body. I quote in this connection the views on this subject held by Corvisart, the practitioner first to employ intelligently the method of percussion for the purpose of discerning cardiac disease. In his epoch-making work, in which are set forth the results of his clinical observations, Corvisart first discusses the relation of the development of anatomy and of pathologic anatomy to diseases of the heart and then proceeds to say:

But it were very erroneous to think morbid anatomy sufficient to accomplish this end; it is quite the reverse; the physician who does not unite physiology [when I say physiology, I mean, once for all, the physiology of experience and observation (ever-cautious of the too easy indications from analogy) but not the systematic physiology which is often supposing, and constantly explaining] with anatomy will ever remain a more or less dexterous, industrious, and patient inquirer, but he will never become a firm and decisive practitioner, particularly in the treatment of the organic lesions.⁴⁹

The facts brought to light by percussion, then, are, in the opinion of the founder of cardiac nosology, of the greatest significance only when viewed from the standpoint of experimental physiology.

Auscultation

Who, if not the practicing physician, would be expected to discover the sounds emitted by the beating heart? The nature of his work requires that the clinician keep alert all of his senses in his effort to bring to light the diseases he may encounter in his practice. The time and energy devoted to human beings for this purpose far exceed those devoted to animals. Yet Harvey, animal experimenter, as well as clinician, seems to have been the first to call attention to the fact that, simultaneously with pulsation, a sound can be heard in the chest.⁵⁰ To the practitioner Laennec, however, belongs the credit of developing clinical auscultation.⁵¹ Whether or not Laennec himself performed experiments on animals I have been unable to determine. As a pupil of Cor-

49. Corvisart: *Essai sur les maladies et les lésions organiques du cœur . . . ,* 1806; transl. by Gates, 1812.

visart (see above) he must, however, have taken at least an active interest in experimental physiology. That he did avail himself of the results of animal experimentation in the interpretation of auscultatory phenomena is seen in the following quotation, which at the same time will serve to indicate that had Laennec had just a little more first-hand knowledge of the action of the heart he might have succeeded in making a better interpretation of the facts revealed by his clinical observations.

At the moment of the arterial pulse the ear is slightly elevated by an isochronous motion of the heart, which is accompanied by a somewhat dull, though distinct sound. This is the contraction of the ventricles. Immediately after, and without any interval, a noise resembling that of a valve, or a whip, or the lapping of a dog, announces the contraction of the auricles. . . . Immediately after the systole of the auricles there is a very short, yet well marked interval of repose. . . . This state of quietude after the contraction of the auricles does not appear to have been known to Haller as a natural condition.⁵²

Laennec therefore accepts without question the fact shown by Harvey and later first utilized by Albertini⁵³ as a diagnostic sign, that the apex-beat occurs with systole; while at the same time he calls attention to what he believes to be an oversight on the part of Haller—by many considered the father of modern experimental physiology—in regard to the time relation of auricular and ventricular systole.

But if Laennec had only taken the pains to examine an exposed beating heart in the light of his clinical observations, he never would have made the mistake of attributing the second sound to the contraction of the auricle, nor would he so quickly have jumped to an erroneous conclusion in the face of the results of direct experimental observation. Not very many years had elapsed, however, when Turner,⁵⁴ interpreting correctly the results of physiologic experiments as recorded in Haller's "Elementa," objected to Laennec's views on the cause of the second sound on the ground that the con-

50. Luciani: *Lehrbuch der Physiologie*, 1905, i, 152.

51. Laennec: *Traité de l'auscultation médiate* . . . , 1819; transl. by Forbes, 1823.

52. Laennec: *Traité de l'auscultation médiate* . . . , p. 256:

53. Quoted by Ziemssen: *Handbuch der speciellen Pathologie*, etc., 1879, vi.

54. Ref. Luciani: *Lehrbuch der Physiologie*, 1905, i, 152.

traction of the auricles precedes that of the ventricles, and does not follow it as Laennec had assumed.

The limits of this paper make it impossible to trace for the reader the development of our knowledge of the cause of the heart sounds.⁵⁵ The statement must suffice that through combined clinical (Laennec, Skoda, etc.) and experimental observation, the most noteworthy of which were made by a committee of the British association under the leadership of Williams,⁵⁶ and the later experiments of Hürthle⁵⁷ and others, we are now quite certain of the true relations which the sounds bear to the events of the cardiac cycle, notwithstanding the existence at the present time of some uncertainty as to the causes of some of the normal sounds. With regard to abnormal heart-sounds, deductions from normal physiology as well as experiments in pathologic physiology have served to indicate to the clinician their meaning and even their diagnostic value. For example, a ringing aortic second sound indicates to the clinician an abnormally high aortic tension. Harvey's experiments in themselves might have suggested this, but the conclusive proof of it was offered by the experiments of Williams and others, who showed that the second sound arises in the arterial valves and that its intensity diminishes when the arterial tension is lowered. If the reader is desirous of further instances of this nature he may consult any of the modern handbooks on diseases of the heart; for example, the article by Gibson on cardiac insufficiency in Osler's "Modern Medicine," which he will find to be practically an article on applied physiology—physiology made up almost exclusively of experiments on animals.

55. An excellent account of this subject is given by Luciani: *Lehrbuch der Physiologie*, 1905, i, 152.

56. Report of the Brit. Assn., 1836, vi, 265.

57. Hürthle: *Arch. f. d. ges. Physiol.*, 1895, ix, 263.

III. CIRCULATORY SYMPTOM-COMPLEXES AND THEIR TREATMENT

An attempt was made in Part II to make it clear that, whereas the attention of the ancients was attracted to certain symptoms, such as palpitation and syncope, owing to their lack of knowledge of the structure and functions of the heart and blood-vessels, such symptoms were not associated with specific diseases of the circulatory system.

CLINICAL CONCEPTS AND ANIMAL EXPERIMENTATION

It has been shown, furthermore, how, in the seventeenth and eighteenth centuries, when post-mortem observations made possible the building of a firm foundation for anatomy and after Harvey's demonstration of the circulation of the blood, the clinical concepts as we now know them began to appear. This fact in itself sufficed to indicate in a general way the dependence of our modern conceptions on the results of experiment. It might, however, be well to call attention to this dependence in somewhat greater detail.

Why valvular defects, both organic and relative, should alter the action of the circulation, and how, becomes perfectly evident when they are viewed in the light of facts demonstrated by experiment. If the lesion causes a stenosis or insufficiency of any valvular orifice, the knowledge of this fact suffices to account for practically all of the signs and symptoms of the disturbed function. Given, for example, narrowing of the mitral orifice, with a knowledge of the physiology of the circulation, the clinical picture is almost completely understood. The relation of the adventitious to the normal heart-sounds, the enlargement of the left auricle, the engorgement of the pulmonary circulation and its consequences, the hypertrophy of the right auricle and ventricle, the pulsation of the liver and of the veins of the neck, as well as other signs and symptoms, become perfectly clear and are seen to be part and parcel of one and the same thing.

The conception of relative or muscular insufficiency of the valvular orifices rests almost entirely on inferences

from results of animal experiments. As long as the Hippocratic idea of the parenchymatous nature of the walls of the heart held sway, the possibility of a variability of the diameters of the cardiac orifices was entirely precluded. When, however, Harvey, Borelli and others¹ recognized that the movements of the heart resembled those of muscles, and after the property of tone in heart muscle had been discovered by Gaskell² the way was opened for the clinical conception of valvular insufficiency due to muscular weakness.

The hypertrophied heart, the *cor bovinum*, as a purely anatomic conception, was one of the earliest cardiac lesions to be described. Suggestions as to its causation were not, however, made until it was recognized that the heart, not the blood, did mechanical work and that the amount of work performed by the heart was subject to variation. Practically the only cause of hypertrophy of voluntary muscle is increased work; then why not of heart muscle, too? When, therefore, a hypertrophied heart is met, the physician, in order to discover the cause, looks for the factor that has increased the work of the heart. Physics teaches that work is proportional to the product of the pressure and the surface. "It is, therefore, not a matter of chance that the first to measure the blood-pressure in animals (Hales) was also the first to attempt the estimation of the work of the heart."³ Since the surface area of the heart and the pressure against which it contracts both are subject to variation, it is to these factors that the clinician looks in order to account for hypertrophies of the heart. In this way many of the etiologic factors of cardiac hypertrophy have been brought to light. It has served to explain the hypertrophies associated with valvular lesions. It has likewise served to explain the cardiac hypertrophy of pulmonary emphysema, of arteriosclerosis, of chronic asphyxia (Hensen⁴), in which condition the blood-pressure is elevated, of many cases of nephritis in all of which the arterial blood-pressure is high, of plethora (which probably increases the work of the heart, not by increasing the blood-pressure, but rather by increasing the amount of blood in, and consequently the area of, the heart (Tigerstedt⁵), and of adhesive pericarditis.

1. See Part II of this article.

2. Gaskell: Jour. Physiol., 1880-82, III, 53.

3. Nagel: Handbuch der Physiologie, I, 866.

4. Quoted by Krehl, Pathologische Physiologie, 1907, p. 32.

The fact that the dilated heart has great difficulty in maintaining the circulation is likewise seen clearly when viewed from the standpoint of mechanical work.

The concept of the weak heart rests on the fact that the heart acts as a force-pump. The signs of failure of the pump, the fall of arterial pressure, engorgement of the veins, etc., are explained by the discovery of Harvey and its elaborations.

Paroxysmal tachycardia is probably merely a symptom of a number of affections of the heart. Through modern clinical methods, which are largely the outcome of work on animals, the behavior of the heart during the paroxysms has been discerned and at least one cause of the symptoms has been determined, namely, pressure on the vagi (see below.)⁶

The investigation of bradycardia has met with better success. There can be recognized by the application to the human being of methods employed in the laboratory: (1) complete bradycardia, that is, slowing of the whole heart and (2) partial bradycardia, by which is understood the slowing of certain parts of the heart below the mouths of the great veins. Clinical experience, in the light of facts accumulated in the laboratory, has led to the recognition of at least two causes of complete bradycardia, namely (a) direct or reflex stimulation of the cardio-inhibitory mechanisms by asphyxia, by arterial hypertension as in acute nephritis,⁷ by increased intracranial tension,⁸ by irritation of the gastro-intestinal canal and peritoneum;⁹ and (b) slowing of the rate of discharge of the mechanism that sets the pace of the heart (Stannius, Gaskell)¹⁰ through the depressing action of poisons or arteriosclerosis. Clinically these two types may be distinguished in man (Dehio) by means of a laboratory test which depends on the fact that atropin paralyzes the vagus terminals in the heart.

Animal experiments (Stannius, Gaskell,¹¹ and others) have brought to light, and have determined the causes

5. Tigerstedt: *Skand. Arch. f. Physiol.*, iv, 41.

6. Hoover: In Osler's *Modern Medicine*.

7. Based on Marey's law, which in turn is based on animal experiments. See *La circulation du sang*, Paris, 1881, p. 321.

8. Cushing: *Am. Jour. Med. Sc.*, 1903, 1017.

9. Based on experiments by Goltz: *Virchows Arch. f. path. Anat.*, 1863, xxvi, 10.

10. Gaskell: Experiments described in *Phil. Tr.*, London, 1882, p. 993.

11. Gaskell: *Jour. Physiol.*, 1883, iv, 61.

of, the type of bradycardia termed incomplete; and the applicability of this work to the condition (Stokes-Adams disease, etc.) as seen in man has been demonstrate by animal experimenters (Chauveau, His, Erlanger¹², etc.) employing in the clinic the methods of the laboratory. These, by showing that the most common form of incomplete bradycardia is atrioventricular heart-block, have very recently served to elucidate a clinical picture that has puzzled the medical world ever since it was first described some seventy years ago.

It is almost too early to predict the outcome of the efforts now being made toward a better understanding of the cardiac arrhythmias. That they have opened a new era in the detection and analysis of cardiac disease is perhaps all that can now be affirmed. However that may be, the result up to date has been that through the clinical application by Wenckebach,¹³ MacKenzie,¹⁴ Hering and others, of facts revealed in the laboratory by Marey, Gaskell, Engelmann, Hering and others, heart irregularities such as extrasystoles, allorhythmia, the absolutely irregular pulse, etc., which heretofore have had no significance whatever, now stand for specific disturbances of the cardiac motor mechanism.

Reference has already been made to the part animal experimentation and experimenters have played in calling the attention of clinicians to the mechanism that comes into play when, as in arteriosclerosis, the arteries become inelastic.¹⁵

Arterial aneurism was recognized in man by the animal experimenter, Galen, and attempts at treatment were made by him. Just what part animal experimentation played in the development of this phase of the subject cannot be determined. However that may be, many signs and symptoms of great significance in the diagnosis of aneurism have since come to the clinician through, or have been rendered clear by, experiments on animals or animal experimenters. Harvey, for example, first called attention to the changes of the pulse. Pressure changes in the arteries have also been detected and for their recognition Williamson finds that "the sphygmo-

12. For the literature see Jour. Exper. Med., 1906, viii, 8.

13. Wenckebach: Die Arrhythmia als Ausdruck bestimmter Functions-Störungen des Herzens, Leipsic, 1903.

14. MacKenzie: Brit. Med. Jour., March and April, 1905.

15. See Part II of this article.

manometer is much more sensitive than the finger."¹⁶ The pupillary effects of aortic aneurism are explained by experiments on the cervical sympathetic, some of which were performed as early as 1727,¹⁷ and by local changes in blood-pressure.¹⁸

The localization of arterial and of most venous emboli from dislodged thrombi is explained perfectly by the circulation. And experimentation has served to throw light on many of the problems connected with the subject of thrombosis. These experiments have demonstrated that slowing of the blood-system *per se* does not cause clotting, although it has been shown by deduction from experiments on animals when the necessary factors are present, decreased velocity plays an important part in thrombosis.¹⁹

ANIMAL EXPERIMENTATION AND THE TREATMENT OF CARDIOVASCULAR DISEASE

To animal experimentation must also be attributed many of the most valuable suggestions as to the treatment of cardiovascular disease. It will, however, be possible to call attention to only a few instances of this most practical phase of the subject.

It is self-evident that with the discovery of the circulation, and only after the elucidation of the part played by the several mechanisms concerned in its maintenance, the rational treatment of the diseases of the circulation by mechanical means became possible.

Then it became possible to appreciate why patients suffering from "delinquum animi or swooning" should be placed in the recumbent position rather than "in an easy erect posture" as suggested by Paul of Ægina and why other practices, some of which are mentioned in Part II, were to be eliminated as irrational.

Bleeding, than which no form of treatment has passed through as many vicissitudes, illustrates how fruitless may be the results of uncontrolled speculation in medicine, the vacillation "in the practice of this therapeutic measure depending intimately on the prevailing views on blood and juices, on fever and inflammation, finally

16. Quoted by Osler: *Modern Medicine*.

17. Petit (1727) and Biffi (1846): Quoted by Schäfer, *Text-Book of Physiology*, ii, 618.

18. Experiments of Wall and Walker; Quoted by Osler: *Modern Medicine*.

19. Baumgarten and Rizor, and von Recklinghausen; Quoted by Blumer: *Osler's Modern Medicine*, p. 505.

on life itself.”²⁰ To-day venesection in diseases of the circulation seems to be indicated in but a single condition which may, however, appear in almost any of the symptom-complexes: “At any stage in a valvular lesion or in hypertrophy and dilatation of the heart . . . acute cardiac insufficiency may arise . . . It is the one condition in which a venesection is advantageous.”²¹ Bleeding, then, is indicated only when it is necessary temporarily to relieve the weakened or dilated heart of the strain under which it is working. The mechanical indication and the mechanical action of bleeding both have been made clear through the discovery of the circulation and the part the heart plays in its maintenance. We no longer hear of bleeding practiced for its “derivatory” and “revulsive” actions.

More is heard to-day of a treatment which is just the converse of venesection, although it is practiced in many conditions to accomplish the very objects that were sought in blood-letting. The use of transfusion as a therapeutic measure was suggested in mythical times as a means of restoring youth. “An experiment which had hitherto only been made in animals,”²² transfusion was first put into practice by Cardanus in the fifteenth century. The attempt did not succeed, however, because, when artery was united to artery, the direction of flow was beyond the control of the surgeon. With the discovery of the circulation, the mechanical requirements of transfusion became clear.²³ Within less than forty years Lower succeeded in transfusing animals by passing the blood from an artery into a vein. And one year later Denis and King, working independently, successfully transfused blood from a lamb into man. The time was not, however, ripe for the practice of transfusion as a therapeutic measure. Unforeseen difficulties arose such as intravascular clotting, clotting at the point of union, and hemolysis. One by one, however, and almost exclusively through animal experimentation, these difficulties were cleared up and then eliminated. The successful efforts to remove what now appears to be the last great difficulty, namely clotting at the point of union, are fresh in the minds of all. Through the

20. Bauer: *Geschichte der Aderlässe*, München., 1870.

21. Osler and Gibson: *Osler's Modern Medicine*, p. 261.

22. Crile: *Hemorrhage and Transfusion*, 1909.

23. I here follow the account given in Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, iii, 87.

use of a method brought to light by animal experiments (Queirolo, Crile),²² of uniting blood-vessels with a tube in such a way that the blood does not come into contact with any foreign surface, or through the use of vessel suture as developed by the experiments of Carrel,²² clotting is no longer to be feared.

Transfusion of blood is used at the present time, however, only as a means of last resort. In most cases the infusion of a salt-solution into the blood vessels accomplishes the same end. The use of this therapeutic measure was suggested by Goltz when he called attention to the fact that the danger of sudden large hemorrhages depends on the emptiness of the heart, which, in that state, cannot do its work efficiently.²⁴ Then, after experiments on animals by Cohnheim (1869) and by Kronencker and Lauder (1879) had demonstrated that the injection of an aqueous solution of sodium chlorid may save the life of an animal which has certainly sustained an otherwise fatal hemorrhage, the measure was tried in surgical and obstetrical practice with the life-saving results that are familiar to all.²⁵

Attention should here be called to the fact that transfusion and infusion experiments represent the first attempts at intravascular medication, a measure that was thereafter extensively employed in the laboratory but which has only recently come into vogue in the practice of medicine.²⁶

Under the caption of mechanical methods of treating cardiovascular disease may also be included resuscitation by means of massage of the heart of subjects in whom the heart has stopped. In the ultimate analysis this method of treatment rests on the fact that the heart acts as a force-pump and that the pumping action of the heart muscle can be replaced for a time by that of the hand of the operator. More specifically, however, direct massage of the heart was first practiced by Schiff, who by this method succeeded in reviving dogs that had been killed with chloroform (1874). The measure was tried in the clinic six years later.²⁷

The drug treatment of diseases of the circulation has been incalculably furthered by means of experiments on

24. Quoted by Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, iii, 92.

24. Quoted by Neuburger and Pagel: *Handbuch der Geschichte der Medizin*, iii, 92.

27. Metcalf: *Boston Med. and Surg. Jour.*, 1909, clxi, 9.

animals, while many of our most useful drugs have been discovered in experiments which were based on a knowledge of the physiology of the circulation.

The medicinal properties of digitalis, the most valuable of heart remedies, were known to the laity and the drug was used by the medical profession long before it was investigated in the laboratory. "The celebrated work of Withering on digitalis, published in 1785, shows," however, "that many deaths were undoubtedly due to the use of digitalis. Indeed, at that time and for half a century thereafter the action of digitalis on the heart and blood vessels was very imperfectly understood."²⁸ Traube's experiments and clinical observations on the action of digitalis did much to increase its use in disease.²⁹ Without going into this subject in any greater detail, the dependence of the physician on practical facts brought to light by means of animal experimentation may be shown merely by giving, in the words of one of the greatest of living clinicians, the main contraindications to the use of digitalis: "It may be said broadly to be contraindicated in all forms of heart disease without symptoms of muscle weakness" and "in states of high arterial tension . . ." ³⁰ The physiologic basis of these physiologic contraindications is so clear as to require no comment whatever.

In the choice of a heart remedy the physician has likewise to be guided by animal experiments. Both digitalis and strophanthin, for example, "act on the heart and on the blood-vessels, but in different degrees, and these differences alone determine whether one or the other shall be used in a given condition. Such differences cannot be determined except by means of animal experiments."²⁸

The use of atropin in cases of overaction of the vagus mechanism is likewise based entirely on experiments on animals.

All of the drugs used as vasodilators, such as nitroglycerin and amyl nitrite, have been discovered by animal experiments and the indications for their use in cardiovascular disease would be meaningless in the absence of facts brought to light through animal experimentation.²⁸ Thus, the nitrates were introduced into

28. Hatcher: Pub. Med. Soc. State of New York, 1909.

29. Ziemssen: Handbuch der speciellen Pathologie, etc., 1879, vi.

30. Osler and Gibson: Modern Medicine, p. 261.

therapeutics by the animal experimenter, Brunton, "who advised their use in angina pectoris to relieve spasm of the arteries." "Besides, in angina pectoris the nitrates may be used in any condition in which it is supposed the arterial tension may be lowered with benefit to the economy," as in certain cases of hypertension, or in combination with digitalis when, in cases of failing heart, the vasoconstrictor action of the latter might embarrass the already overtaxed heart.³¹

The vasoconstrictor adrenalin, one of the most valuable of recently discovered drugs, was brought to light through animal experimentation.³² Indeed this statement is true of other drugs, too numerous to be mentioned here.

Animal experimentation on the circulation has also proved of value in the standardization of cardiovascular remedies. It is by that method alone that the physiologic activity of digitalis and strophanthus preparations, for example, can be determined, it is by that method alone that the physician can be supplied with digitalis and strophanthus preparations which will be of uniform strength and on which he can positively rely.³³

The treatment of surgical diseases of the heart has been incalculably furthered—indeed this phase of medicine practically has been opened—by the experimental development of methods of opening the thorax under a negative³⁴ or a positive³⁵ pressure. Nor should we lose sight of the fact that both of these methods have as their foundation the animal experiments of Lower and of Haller, which were the means of laying down the first principles of the mechanics of respiration.³⁶

THE WIDE INFLUENCE OF THE DISCOVERY OF THE CIRCULATION.

Physicians should be reminded of the fact that the discovery of the circulation has benefited not only the specialist in diseases of the circulation; it has made itself felt in practically every branch of physiology and

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- 31. *Cushny: Text-Book of Pharmacology and Therapeutics*, 1906.
 - 32. *Oliver and Schaefer: Jour. Physiol.*, 1895, xviii, 230.
 - 33. *Edmunds, Charles Wallis: The Standardization of Cardiac Remedies, THE JOURNAL A. M. A.*, May 25, 1907, xlviii, 1744.
 - 34. *München. med. Wchnschr.*, 1906, liii, 1.
 - 35. *Deutsch. med. Wchnschr.*, 1906, p. 534.
 - 36. *Neuburger and Pagel: Handbuch der Geschichte der Medizin*, ii, 341 and 351.

through these branches in practically every branch of medicine. To give but a single case in point. The knowledge of the circulation as acquired through animal experimentation led physiologists to study function in isolated organs kept alive by means of an artificial circulation. Using this method von Schröder, for example, determined the role of the kidneys in the process of urea formation and elimination.³⁷ These experiments, by placing the treatment of diseases of the kidney on a rational basis, have been of incalculable value to the clinician.

THE LYMPHATIC SYSTEM.

The lymphatic system, as tributary to the circulatory system, should perhaps receive a word of notice here. Briefly, then, it may be said that in this connection the physician owes everything to animal experimentation, since the lymphatics were discovered by Aselli (1622) in an experiment on a living animal.³⁸

And, it may furthermore be added, one of the chief practical uses to which the lymphatics are put by the physician, namely, the hypodermic administration of drugs, suggested itself to Wood in 1855 through contemplation of an animal experiment performed by Müller.³⁹

148 West Gorham Street.

37. Von Schröder: Arch. f. exper. Path. u. Pharmakol., 1882, xv, 364; and 1885, xix, 373.

38. Neuburger and Pagel: Handbuch der Geschichte der Medizin, II, 336.

39. Wood: A New Method of Introducing Medicines into the System, Month. Jour. Med., 1855, xx, 183.

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What Vivisection Has Done for Humanity

W. W. KEEN, M.D., LL.D.

PHILADELPHIA

DEFENSE OF RESEARCH PAMPHLET XIV

Issued by the Council on Defense of Medical Research
of the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
1910

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535 Dearborn Avenue

Chicago, Illinois

What Vivisection Has Done for Humanity

W. W. KEEN, M.D., LL.D.

PHILADELPHIA

WHAT VIVISECTION HAS DONE FOR HUMANITY*

W. W. KEEN, M.D., LL.D.
PHILADELPHIA

PREFACE

It is not too much to say that Dr. Keen, of Philadelphia, is universally regarded to-day in the world of surgery as the foremost of living American surgeons. The leading universities and academies of science of the United States, England, France and Germany have honored him with their degrees and honorary titles, and the published works on surgery, written and edited by him, are accepted as standard authorities by the profession in which he has gained such eminent distinction. Dr. Keen is, therefore, as well, if not better, qualified to present the advantages of vivisection as any American writer on the subject.—THE EDITORS of *the Ladies' Home Journal*.

In 1905 I had made all my arrangements to do an operation on a Thursday morning. Among my assistants was Dr. C. On Wednesday morning he telephoned and said he was not feeling very well and that I had better engage some one to take his place. This I did, giving no special thought to the matter, supposing it was an unimportant passing illness. At ten o'clock that same night I was startled by a telephone message that if I wished to see Dr. C. alive I must come at once! In a few minutes I was there, but he was already unconscious. As I sat beside him and his weeping young wife, who soon expected to become a mother, how I longed for some means by which the hand of death could be stayed; but he died in less than thirty-six

* Reprinted, by permission of the Editor, from the *Ladies' Home Journal*, April, 1910.

hours from the time that he was seized with cerebro-spinal meningitis.

On June 16, 1909, Charles E. Hughes, Jr., son of the governor of New York State, and president of his class, was graduated at Brown University. A few weeks earlier he had been suddenly seized with a violent attack of the same disease—cerebrospinal meningitis. When some of the fluid around his spinal cord was removed by “lumbar puncture”—that is, puncture of the spinal canal in the small of the back by a hypodermic needle—there settled to the bottom of the test-tube a half inch of pure pus (“matter”). No medical man familiar with this terrible disease would have thought it possible that he could recover when such a condition existed. But in 1907, midway between the death of Dr. C. and the case of young Hughes, Drs. Flexner and Jobling, of the Rockefeller Institute, had discovered by researches on animals alone a serum against this disease. Three doses of this serum were administered also by “lumbar puncture” to young Hughes. Within twenty-four hours after the first dose his temperature fell to normal. The pus disappeared after the second dose and he soon recovered and was able to take his degree in the presence of his proud father. The tragedy in the case of Dr. C. was averted, a useful life was spared, and a family made happy.

GREAT DECREASE IN MORTALITY FROM CEREBROSPINAL MENINGITIS

In discovering this serum Dr. Flexner experimented on twenty-five monkeys and one hundred guinea-pigs. Many of these animals themselves had been cured by the use of the serum. Having, therefore, found it effective in animals he proceeded to test it on human beings. Before the introduction of the serum, medicine was almost helpless. Whatever treatment was adopted seventy-five to ninety patients out of one hundred were sure to die. In two years this serum has been used in this country and in Europe in about one thousand cases. In these one thousand cases the mortality has dropped to thirty, twenty, ten, and even to seven in a hundred. If we take the mortality of the days before the serum treatment was used at 75 per cent., and the mortality since it was discovered at 25 per cent., there is a clear saving of 500 human lives!

Not only have 500 human lives been saved in these first one thousand cases, but for all time to come in every thousand 500 more human lives will be saved.

Moreover, we must not forget that these thousands who would die were it not for Dr. Flexner's serum had families and friends who would have been filled with sorrow, and, in case it was the breadwinner of the family whose life was lost, would have had to suffer the deprivations and pangs of poverty.

Let me now put a plain, straightforward, common-sense question. Which was the more cruel: Doctor Flexner and his assistants who operated on twenty-five monkeys and one hundred guinea-pigs with the pure and holy purpose of finding an antidote to a deadly disease and with the result of saving hundreds, and, in the future, of thousands on thousands of human lives; or the women who were "fanned into fury" in their opposition to all experiments on living animals at the Rockefeller Institute, "no matter how great the anticipated benefit"?

If these misguided women had had their way they would have nailed up the doors of the Rockefeller Institute, would have prevented these experiments on 125 animals, and by doing so would have ruthlessly condemned to death for all future time 500 human beings in every one thousand attacked by cerebrospinal meningitis!

If your son or daughter falls ill with this disease to whom will you turn for help—to Flexner or to the anti-vivisectionists?

Of these one hundred and twenty-five animals, as a rule those which died became unconscious in the course of a few hours and remained so for a few hours more till they died. They suffered but little. When they died they left no mourning families and friends. They left undone no deeds of service or of heroism to either their fellows or to the human race, as the human beings whose lives were rescued by their death may do. But these deluded women had their minds so centered on the sufferings of these one hundred and twenty-five animals that their ears were deaf and their hearts steeled against the woes and the sufferings of thousands of human beings, their families, and their friends. Is this common-sense? Are not human beings "of more value than many sparrows"?

EXPERIMENTS IN SEWING BLOOD-VESSELS END-TO-END

Less than two years ago their first baby was born to a young doctor and his wife in New York City. Scarcely was the child born before it began to bleed from the nose, the mouth, the gums, the stomach and the bowels. It was a case which we known as "hemorrhage of the newborn," which attacks about one baby in every thousand. It is very frequently fatal, and in treating it up to that time physicians practically groped in the dark, trying one remedy after another, but, alas, too often in vain!

The bleeding continued. This poor little baby soon showed the pallor which accompanies severe loss of blood. It lost all appetite, was suffering from high fever, and, finally, by the fourth day the physician in attendance told the parents frankly that the child could live only a few hours. Then, in the dead of the night the father wakened Dr. Carrel, one of the assistants in the Rockefeller Institute. The father lay down alongside of his firstborn. The artery of the pulse in the father's arm was laid bare and sewed end-to-end to a vein in his baby's leg, and the blood was allowed to flow from father to child. The result was most dramatic. A few minutes after the blood began to flow into the baby's veins, its white, transparent skin assumed the ruddy glow of health, the hemorrhage from every part of the body ceased instantly and never returned, and, as Dr. Samuel Lambert, who reports the case, puts it, there was no period of convalescence; immediately before the operation the baby was dying; immediately after the operation it was well and strong and feeding with avidity. That baby to-day, after two years, as I know personally, is a splendid specimen of a healthy child.

Perhaps my readers may see nothing very wonderful in this, but we surgeons know that it is one of the most remarkable recent achievements in surgery. For many years we have been trying to devise a method by which we could sew severed blood-vessels end-to-end without danger to the patient. The difficulty has always been that, no matter what were the methods employed, the blood nearly always formed clots at the roughened ring where the two ends of the divided blood-vessel were sewed together. These clots passed up to the heart and into the lungs of the patient and produced pneumonia, so that the old method of transfusion of blood has been

practically abandoned for years. Dr. Carrel worked out his new method on the blood-vessels of dead human beings, and, when it seemed to him to be satisfactory, put it to the proof on two living dogs, and then used it in living human beings. It is now in use everywhere.

Moreover, Dr. Crile, of Cleveland, who has so splendidly enlarged our means of coping with disease, has used the same method in another way. When patients come to him too weak to be operated on and ordinary tonics and food do not strengthen them, he has transfused the blood from husband, father or son, and thus given the patient sufficient strength to bear the operation. He has used even a more striking method. For example when a woman has to be operated on—say for cancer of the breast—and is so weak that the shock, the anesthetic and the loss of blood would probably turn the scale against her, he has had the husband lie down alongside of her, has sewed the artery of the pulse of the husband to a vein in his wife's leg and allowed the blood to flow. In a few minutes, when she has become strong enough, he has etherized her and proceeded with the operation, starting or stopping the flow of blood according to the varying needs of the patient. At the end of the operation, through the new life-blood that has been given her, the patient has been in better condition than when the operation began. These methods, too, are now in successful use by other surgeons.

Let me again put the plain, straightforward, common-sense question: Who is the more cruel: Dr. Carrel, in devising this life-saving method of transfusion of blood by experimenting on two living dogs, and saving through himself and other surgeons scores of lives already, and even thousands in the future; or the women who would shackle him, shut up the Rockefeller Institute and thrust these poor patients into their graves? Does not the work of Drs. Flexner, Jobling and Carrel and their assistants not only justify the existence of the Rockefeller Institute, but also bid us tell them Godspeed in their mission of mercy, and give them and those engaged in similar blessed work all over the world our confidence, encouragement and aid? Is it just, is it fair, is it Christian to call such an institution a "hell at close range," as the Rockefeller Institute is called in a pamphlet written by a woman and distributed by antivivisectionists?

ANTISEPTIC EXPERIMENTS WERE FIRST TRIED ON
ANIMALS

I suppose that in this day of general intelligence scarcely any person, if he or she had to submit to an operation, would be willing to have it done by a surgeon who did not use antiseptic methods. These methods we owe to Lord Lister of London, still living in his eighty-third year. Few of my readers, however, know how enormous the contrast is between the days before Lister's discoveries and the present. I was graduated in medicine in 1862. The antiseptic method was adopted by various surgeons, we may say roughly, between the years 1875 and 1880. Prior to 1876 I practiced the old surgery, but ever since then the new antiseptic method. I passed through the horrible surgery of the Civil War, when blood-poisoning, erysipelas, lockjaw, hospital gangrene and all the other fearful septic conditions were every-day affairs. In five hundred and five cases of lockjaw during the Civil War four hundred and fifty-one patients died. In wounds of the intestines the mortality was ninety-nine out of a hundred. In sixty-six cases of amputation at the hip-joint fifty-five patients died. In one hundred and fifty-five cases of trephining ninety-five patients died. After the war for some years I was an assistant of Dr. Washington L. Atlee. A more careful surgeon I never saw, but two out of every three of his patients died. There are now many surgeons who can show series of hundreds and even thousands of cases of ovariotomy and other abdominal operations with a mortality of only five in a hundred, and some of only one in a hundred. After "clean" operations—that is, with no "matter" present—blood-poisoning, lockjaw and erysipelas are well-nigh unknown, and I have not seen a single case of hospital gangrene in the thirty-five years since I adopted the antiseptic method.

One of the most common operations is amputation of the breast for cancer, in which now we do far more extensive operations than formerly. These operations are followed by permanent cure in more than one-half of the patients operated on early, and rarely more than one or two women in every hundred die. Recovery also follows in a few days and not seldom with but little pain, instead of several weeks or even months of great suffering as before the days of antisepsis.

All of this wonderful improvement we owe to Lord Lister and the new science of bacteriology which treats of "bacteria" or "germs." Both Lister's work and that of the bacteriologist are and must be absolutely founded finally on experiments on animals. The laboratory was of use, but, in order to be absolutely certain that he was right he had to experiment on a few animals—the only possible way of achieving positive knowledge.

Who, I ask, are the more humane: Lord Lister and other surgeons who have made these life-giving, pain-saving experiments on animals, or those who—if they had succeeded in the past in prohibiting such experiments—would have compelled surgeons in 1910 to continue to use the same old, horrible, dirty methods of surgery as in the days before Lister, and thus to offer up hecatombs of human lives to the Moloch of antivivisection? Which method will any man of common sense or any woman with a human heart choose?

HOW THE SCOURGE OF MOTHERHOOD HAS BEEN BANISHED

Even in surgery it is doubtful if a more wonderful improvement has been realized than in our maternity hospitals and in private obstetric practice as a direct result of the work of Pasteur and Lister. Well do I remember as a young man every now and then an outbreak of that frightful and fatal puerperal or "child-bed" fever in our maternity hospitals. Almost every woman who then entered such a hospital was doomed to suffer an attack of the fever, and its mortality sometimes ran up to seventy-five, or even more, out of every hundred mothers. Often such hospitals had to be closed till the then unknown poison disappeared. Not a few obstetricians had to quit practice entirely for weeks because every woman they attended fell ill of the disease and many, many died. Finally Pasteur appeared on the field. In 1878, in a discussion on puerperal fever at the Paris Academy of Medicine, after a member had eloquently discussed various alleged causes of these epidemics, Pasteur interrupted him and said: "All this has nothing to do with the cause of these epidemics. It is the doctors who transport the microbe from a sick woman to a healthy woman." When the speaker responded that he feared they would never find this microbe Pasteur immediately advanced to the blackboard, drew the picture of what we know as the "streptococcus" and said: "This is the cause of the

disease." This recognition of the streptococcus as the cause of puerperal fever and the consequent adoption of antiseptic methods have practically abolished puerperal fever and reduced the mortality in maternity cases to less than one in a hundred.

All this we owe absolutely to experiment on animals. Nothing else could have given us the knowledge. Even the horrible experiments that were being made by doctors who were ignorantly spreading the poison all around them, even these were not sufficient to open our eyes to the real cause of the disease. The laboratory test-tubes and experiments on animals were the chief means by which this scourge of motherhood has been banished.

EXPERIMENTS ON MAN HAVE VANQUISHED YELLOW FEVER

In addition to all these another fearful disease, yellow fever, has also been abolished by experiment which was necessary for the final convincing proof. I need not repeat at length the frightful ravages of this terrible pestilence in days gone by. Cuba was never free from it for nearly two centuries until the American Commission showed how to get rid of it. The Panama Canal Zone had perhaps the worst reputation in the world as a graveyard for strangers, and now for four years not a single case of yellow fever has originated there! Colonel Gorgas has made the Panama Canal a possibility.

I wish that every one might read that most interesting little book, "Walter Reed and Yellow Fever," by Dr. Howard A. Kelly, and see the wonderful methods by which this scourge of humanity has been abolished. When one thinks of the enormous difficulties of the problem the wonder is that it was ever solved. There are about 400 hundred varieties of mosquito. Only one of them carries the poison of yellow fever. Of this variety only the female carries the poison, and this female mosquito must have bitten a patient sick with yellow fever during the first three days of his illness, or she could not become infected. Moreover, after infection, the poison, whatever it is, does not develop in the body of the female mosquito for about twelve days. These facts were thought to be true, but there was no

~~positive proof~~ A very large number, perhaps the majority, of yellow-fever experts still believed that the disease was carried in clothing, bedding, etc. To disprove this experiments were tried first of all by doctors on themselves. They slept in the beds in which yellow-fever patients had died, and in their very clothes, night after night—clothes soiled with their black vomit, urine and feces. At other times doctors have actually swallowed the black vomit, tried to inoculate themselves by putting some of it into their eyes, by hypodermic injections, etc., in the vain attempt to discover the cause of the disease and the means by which it was spread, hoping in this way to discover the means of preventing it. Surely self-sacrifice could go no further. Yes, it could go further. One more step was requisite. The only way to give the absolute final proof was for a well man to be bitten by a mosquito known to be infected. Dr. Carroll, of the United States Army, was the first one who offered himself. Other men followed—doctors, soldiers and others. Several lost their lives, among them Dr. Lazear at the beginning of a most promising career. His tablet in the Johns Hopkins Hospital, in the fine words written by President Eliot, records that "With more than the courage and the devotion of the soldier he risked and lost his life to show how a fearful pestilence is communicated and how its ravages may be prevented."

It is often said that such experimental work brutalizes men. Let us read a letter from Dr. Reed to his wife, remembering, also, that the same high and holy purposes animate Doctors Flexner, Carrol, Crile and other experimenters:

QUEMADO, CUBA, 11:50 p. m., Dec. 31, 1900.

Only ten minutes of the old century remain. Here have I been sitting, reading that most wonderful book, "LaRoche on Yellow Fever," written in 1853. Forty-seven years later it has been permitted to me and my assistants to lift the impenetrable veil that has surrounded the causation of this most wonderful, dreadful pest of humanity and to put it on a rational and scientific basis. I thank God that this has been accomplished during the latter days of the old century. May its cure be wrought out in the early days of the new! The prayer that has been mine for twenty years, that I might be permitted in some way or at some time to do something to alleviate human suffering, has been granted!

This prayer of Reed—that its cure might be wrought out in the new, the twentieth century—has been abundantly realized and yellow fever is now a vanquished foe.

Unfortunately, the lower animals cannot be infected with yellow fever. If they could be Lazear and the other victims would have been saved. But they, yielding up their lives as leaders of a forlorn hope in the battle against disease, have made it possible to free the world from this dreadful scourge. Never was there a finer exhibition of courage!

WHY MODERN SURGERY IS SUCCESSFUL IN BRAIN DISORDERS

A few years ago I was called to Annapolis to see a young man who had been injured in a football game. He was evidently swiftly going to his grave. He had certain peculiar symptoms, which, in the light of cerebral localization—that is, the fact that certain definite portions of the surface of the brain have each a certain definite function—I believed to be due to a clot of blood inside of his head above his left ear. There was a bruise, not above the ear, but at the outer end of the left eyebrow. Before 1885 I should have opened his skull under the bruise—apparently the almost certain point of injury—would have failed to find the clot, and he would surely have died. Instead of this I made a trap-door opening 3 inches away from this bruise, removed nine tablespoonfuls of clotted blood, closed the wound so that his skull was as firm as ever, and he recovered, continued his studies, was graduated from the Naval Academy. Lately he has heroically given up his life at the call of duty. Had it not been for experiments on animals which had definitely fixed certain spots in the brain as the centers for movements of the hand, arm, shoulder, head, face, etc., it would have been utterly impossible for me to save his life. This is but one of hundreds of similar cases in which modern surgery deals with tumors of the brain, hemorrhage inside of the skull and many other disorders, and deals with them successfully.

THE GREAT BLESSINGS OF ANTITOXIN IN DIPHTHERIA

I have heard the following pitiful story from one of my colleagues. He and a young mother stood by the bedside of her only child. The child, in the throes of diphtheria, was clutching at its throat and gasping

vainly for breath. Suddenly the mother flung herself on the floor at the doctor's feet in an agony of tears, entreating him to save her child. But alas! it was impossible. Had this case occurred a few years later, however, when the blessed antitoxin for diphtheria had been discovered (solely by animal experimentation), this remedy would have been given early; and almost certainly within a few hours the membrane would have softened and disappeared, and that life, precious beyond rubies, might have been saved.

In those early dreadful days the only comfort we could give such distracted mothers—possibly some of them may read these very lines—was that “it was God’s will.” Yes! Then, possibly, it was God’s will; but now, thank God, it is not His will. One might as well say it is God’s will that thousands should die from smallpox when vaccination will protect them; that other thousands should die from typhoid fever when a pure water-supply and the banishment of the fly will prevent it; that thousands of women should die from puerperal fever when sterile hands and sterile instruments will save them!

Let me give a table of some official reports showing in nineteen American and European cities the mortality in every 100,000 inhabitants from diphtheria in 1894—that is to say, before the use of the antitoxin of diphtheria—and in 1905, when its use had become general. Being official and from nineteen cities in America and Europe, its accuracy can hardly be assailed.

TABLE OF MORTALITY FROM DIPHTHERIA

	Per 100,000 Inhabitants.	
	1894.	1905.
New York	158	38
Philadelphia	128	32
Baltimore	50	20
Boston	180	22
Brooklyn	173	43
Pittsburg	64	26
London	66	12.2
Paris	40	6
Vienna	114	19

These nine and ten other large cities taken together average as follows; in 1894, 79.9, and in 1905, 19, per 100,000 inhabitants—that is to say, in these nineteen cities the average death rate in 1905 was less than one-fourth of the rate before the introduction of the serum treatment.

VIVISECTION IS NEVER UNNECESSARILY CRUEL

The alleged atrocities so vividly described in antivivisection literature are fine instances of "yellow journalism," and the quotations from medical men are often misleading. Thus, Sir Frederick Treves, the eminent English surgeon, is quoted as an opponent of vivisection in general. In spite of a denial published seven years ago the quotation still does frequent duty. I know personally and intimately Horsley, Ferrier, Carrel, Flexner, Crile, Cushing and others, and I do not know men who are kinder and more lovable. That they would be guilty of deliberate cruelty I would no more believe than that my own brother would have been.

Moreover, I have seen their experiments, and can vouch personally for the fact that they give to these animals exactly the same care that I do to a human being. Were it otherwise their experiments would fail and utterly discredit them. Whenever an operation would be painful an anesthetic is always given. This is dictated not only by humanity, but by two other valid considerations: first, long and delicate operations cannot be done properly on a struggling, fighting animal any more than they could be done on a struggling fighting human being, and so again their experiments would be failures; and second, should any one try an experiment without giving ether he would soon discover that dogs have teeth and cats have claws. Moreover, it will surprise many of my readers to learn that of the total number of experiments done in one year in England 97 per cent. were hypodermic injections and only 3 per cent. could be called painful!

If any one will read the report of the recent British Royal commission on Vivisection "he would find," says Lord Cromer, "that there was not a single case of extreme and unnecessary cruelty brought forward by the Antivivisection Society which did not hopelessly break down under cross-examination."

EXPERIMENTAL RESEARCH IS OUR DUTY

In view of what I have written above—and many times as much could be added—is it any wonder that I believe it to be a common-sense, a scientific, a moral and a Christian duty to promote experimental research? To hinder it, and, still more, to stop it would be a crime against the human race itself, and also against

animals, which have benefited almost as much as man from these experiments.

What do our antivivisection friends propose as a substitute? Nothing except clinical—that is, bedside—and post-mortem observations. These have been in use for two thousand years and have not given us results to be compared for a moment with the results gained by experimental research in the last fifty, or even the last twenty-five years.

Finally, compare what the friends and the foes of research have done within my own professional lifetime. The friends of research have given us antiseptic surgery and its wonderful results in every region and organ of the body; have abolished, or nearly abolished, lockjaw, blood-poisoning, erysipelas, hydrophobia, yellow fever; have taught us how to make maternity almost absolutely safe; how to reduce the mortality of diphtheria and cerebrospinal meningitis to one-fourth and one-third of their former death-rate, and have saved thousands of the lower animals from their own special diseases.

What have the foes of research done for humanity? Held meetings, called the friends of research many bad names and spread many false and misleading statements. Not one disease has been abolished, not one has had its mortality lessened, not a single human life has been saved by anything they have done. On the contrary, had they had their way, puerperal fever and the other hideous diseases named above, and many others, would still be stalking through the world, slaying young and old, right and left—and the antivivisectionists would rightly be charged with this cruel result.



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The Relation of Animal Experimentation to Our Knowledge of Plague

G E O R G E W. M c C O Y, M.D.

Passed Assistant Surgeon, U. S. Public Health and Marine-Hospital Service

SAN FRANCISCO

DEFENSE OF RESEARCH PAMPHLET XV

Issued by the Council on Defense of Medical Research
of the American Medical Association

"The humanity which would prevent human suffering is a deeper and truer humanity than the humanity which would save pain or death to animals."—*Charles W. Eliot.*

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THE RELATION OF ANIMAL EXPERIMENTATION TO OUR KNOWLEDGE OF PLAGUE

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SAN FRANCISCO

Comparatively few diseases of man are readily transmitted to laboratory animals. In plague, however, we have an infection that can be reproduced in many of the animals ordinarily used for experimental purposes. The question then arises as to whether we know more about this disease than we do about infections that are less readily transmitted to animals, and those that thus far have not been studied in the lower animals. In reply it may be pointed out how much more accurate knowledge we have of the essential cause of plague epidemics than we have of outbreaks of typhoid fever, scarlet fever, measles, typhus fever and others that might be mentioned. When plague is to be combated, there need be no speculation as to the source of the infection. The outbreaking is not to be attributed to such vague and indefinite sources as impure air, a bad water supply, or a mysterious contagious influence; but we know that the problem is the simple and direct one of eliminating the infected rodent. Attention may be called to the fact that fortified by our knowledge of this disease, much of which has been gained by animal experimentation, we are able to take such effective measures against its spread that, at the present day, plague in a community may be promptly controlled and even eradicated. In substantiation of this statement, the epidemics that have occurred at various times in the past few years in Oporto, Rio Janeiro, Glasgow, Liverpool and other cities abroad, and in San Francisco and Seattle in the United States may be cited. It is not too much to say that without the knowledge of the disease gained from animal experimentation these sanitary

victories would not have been won. It is quite true that, even with this knowledge, little can be accomplished unless we have the intelligent assistance and cooperation of the community afflicted. In contrast to the splendid achievements in the cities mentioned we may cite countries where plague annually claims an enormous toll of human life; for example, India, where fanaticism manifests itself in the form of a violent antagonism to the sacrificing of lower animals for any purpose, even such a laudable one as the suppression of a disease that on several occasions has claimed over one million victims per year. In China, there is no such antipathy to the taking of life of the lower animals, but there is found an ignorance and apathy most effective in nullifying any efforts looking to an improvement of sanitary conditions and surroundings.

Our knowledge of the cause of plague dates from the work of Yersin,¹ and of Kitasato² in Hong Kong. These investigators, working independently, discovered the micro-organism that has since come to be universally recognized as the cause of the disease. They isolated the organism from the sick and from the bodies of persons who had died of the disease. The opportunity of reproducing the infection in laboratory animals was requisite to complete the chain of evidence necessary to establish the relation of the germ to the disease.

Prior to the work of the investigators mentioned, epidemics of plague were attributed to telluric and climatic conditions, to soil infection and to other sources. As a result of these erroneous views, intelligent measures looking to the suppression of the disease were impossible. The vigorous quarantines that were inaugurated, by reason of the hardship they inflicted, defeated the very purpose for which they were established.

Since the discovery of the actual causative agent of the disease, *Bacillus pestis*, progress in solving many of the problems has been rapid, and it may be asserted without fear of contradiction that every material advance has been made possible by the facts demonstrated by means of animal experiments. The subject will be considered first in the more important aspect, namely,

1. Yersin : Ann. de l'Inst. Pasteur, 1894, viii, 662.
2. Kitasato : Lancet, London, 1894, ii, 428.

the infected rodent, by means of which the disease is transferred from place to place and is spread in communities; and second, in relation to the preventing of the infection of individuals and in curing the sick.

RELATION OF RODENTS TO PLAGUE

Prior to the discovery of the organism causing the disease, the association of rat epizootics with outbreaks of human plague had been noted by several observers. That the oft-cited biblical verses,³ which mention "emeroths" and "mice," really referred to the association of plague and rats cannot be demonstrated; and the other early records are also the subject of much difference of opinion. The actual relation between the disease in rodents and that in man, however, had never been established. It was most important to prove this point, and to discover the actual manner in which the disease was spread among the rodents, and if possible, the manner in which man was infected from rodents. To these problems several investigators turned their attention. It is needless to point out that these questions could not be settled without recourse to animal experiments.

The earlier workers had found the plague bacillus in the bodies of insects that had fed on the blood of animals sick of the disease but it remained for Simond⁴ to actually convey plague from one animal to another by means of insects (fleas). Simond found that when fleas were placed on a plague-infected rat they drew blood containing the plague bacillus, and that by transferring these infected fleas to a healthy rat the disease could be transmitted. Subsequently certain observers failed to confirm this work, but as is so often demonstrated, one properly controlled positive result is of more value than many negative ones. Simond's work was confirmed by Verjbitski⁵ who succeeded in transferring the infection from rodent to rodent by means of fleas and other insects. Verjbitski's results were verified for the most part by the investigators of the Advisory Committee appointed by the Secretary of State for India, the Royal Society and the Lister Institute.⁶ By means of an extensive series of experiments these observers found that plague infection would not spread

3. Samuel, vi, 5, 11.

4. Simond: Ann. de l'Inst. Pasteur, 1898, xii, 625.

5. Verjbitski: Transl. in Jour. Hyg., 1908, viii, 162.

6. Jour. Hyg., 1906, vi, 421.

among rats except in the presence of fleas. The same fact was found to hold good in the case of guinea-pigs. In other words, it was found that healthy rats and healthy guinea-pigs might be kept in close contact with plague sick rodents, but that the disease was never transmitted to the well ones unless fleas were present. While this evidence was of great value in throwing light on the probable mode of transmission of the disease from rodents to man, or possibly from man to man, it was desirable to conduct experiments with animals more closely related to human beings, and for this purpose monkeys were used.⁷ The monkeys were placed in cages in such a way as to simulate so far as possible the conditions under which man might be brought in relation to fleas from infected rodents. It was found that it was possible in this manner to convey plague to the monkeys.

Other most instructive and interesting experiments were performed by placing guinea-pigs in houses where plague cases had occurred, or where plague rats had been found. Many such houses were found to be infected as was shown by the fact that the guinea-pigs died of plague, and plague-infected fleas were found on them. In addition to these animal experiments, epidemiologic observations were carried out which together with the laboratory observations go far towards showing that, at least in India, the great majority of cases of plague are due to infection of man from rats through rat fleas.

Part of the work of this committee has been repeated by Kitasato⁸ who reaches the conclusion that in Japan in the majority of cases the infection is conveyed in the same way as in India.

It may be thought that the presence of an epidemic among rodents under natural conditions would be manifested by so large a mortality among these animals as at once to make manifest the presence of the disease. Such, however, is not the case; it is exceptional to find a death-rate among the rodents large enough to attract the attention of the casual observer. With the exact knowledge of the mode of the conveyance of the infection and its relation to rats, the lines along which work must be performed to control an epidemic become well defined.

7. Jour. Hyg., 1906, vi, 464; 1907, vii, 432.

8. Kitasato: Ztschr. f. Hyg. u. Infektionskr., Nov. 26, 1908, p. 279.

The demonstration of the relation of the disease in man to that in the rat, and the mode of conveyance from the latter to the former, explain many of the facts long known about plague epidemics such as the lack of contagiousness, the gradual, almost mysterious, spread through a community and through a country.

The measures for the control of a plague epidemic do not come within the scope of this paper, but we may state that they are essentially the ridding of a community of infected rats. We may be pardoned for emphasizing here what has been so often pointed out, that plague is not a "filth disease" in the ordinary sense of the term. Plague in human beings is definitely associated with the same disease in rodents, and ordinary sanitary measures have comparatively little influence on its spread. It can be controlled and prevented only by measures directed to the actual cause, the infected rodents.

What has been said thus far refers particularly to the bubonic type of plague, which is by far the most common in all epidemics and in all countries. The pneumonic type of the infection is also very important, especially for the reason that it is directly contagious from person to person, and has claimed many physicians and nurses for its victims. This type of the disease was described by the German plague commission⁹ and by Childe¹⁰ and its origin traced to the same micro-organism that is responsible for the more common bubonic type. It would have been impossible to prove that the pneumonic form of the disease was due to the plague bacillus but for the valuable assistance rendered by the methods of animal inoculation. Only less important than the relation of rat plague to human plague is the relation of plague in ground-squirrels to the same disease in man. This is especially true in America, for it is established beyond question that cases of plague in human beings have been derived from ground-squirrel infection.¹¹ It would have been impossible to prove the presence of plague among ground-squirrels on the Pacific Coast without resorting to animal experiments. Who would have accepted the diagnosis of squirrel plague had it been based on morphologic and cultural studies alone? Certainly no trained observer and probably no

9. Deutsch. med Wchnschr., 1897, xxiii, 301.

10. Childe: Brit. Med. Jour., 1897, i, 1215.

11. Jour. Infect. Dis., Dec. 18, 1908, p. 485; Pub. Health Rep., Jan. 14, 1909, p. 27.

intelligent layman. It has often been found that the demonstration of plague in laboratory animals carries to the mind of the layman a conviction that nothing else will.

In most countries and in most communities the announcement of the presence of plague is a signal for a violent denunciation of those who have discovered or announced the presence of the disease; and if one were compelled to rely on methods of investigation other than the inoculation of animals it is probable that skeptics would never be convinced. It is most gratifying, and an evidence of the rapid progress in sanitary matters, that since the first announcement of plague among ground squirrels on the Pacific coast¹² no voice has been raised to question the diagnosis.

Two methods of inoculating laboratory animals with plague are in common use. The one is by the use of the ordinary hypodermic syringe; the second, usually known as "vaccination" or Kolle's method, requires simply the shaving of the skin and the rubbing of the suspected tissue or culture on the shaven area. Neither method is painful.

Now as to the use of laboratory animals in establishing the diagnosis of plague in persons or in rodents: In the majority of cases of plague a probable diagnosis can usually be made by clinical and microscopic methods; but in other cases it is necessary to resort to animal inoculations. Especially in the case of plague in rodents, resort to animal tests frequently becomes indispensable, as the tissues are apt to be invaded by other micro-organisms which speedily outgrow the plague bacillus so that methods other than the inoculation of animals are likely to fail. It is obvious that in order that measures looking to the protection of persons may be taken, a positive diagnosis is essential.

Animal experimentation is the only means at our disposal for determining the species that are susceptible to the disease, and thus learning which animals must be regarded with suspicion and which may be eliminated from consideration as possible agents in spreading the disease. This may be illustrated by two examples:

The first relates to the gopher, a very common rodent. When the squirrel-plague campaign was begun on the Pacific coast, the question arose as to whether it was

necessary to destroy gophers as well as ground-squirrels. As a result of certain experiments that had previously been made with gophers at the Plague Laboratory, it was proved that the susceptibility of these rodents was so slight as to make it unlikely that any measures would need to be taken against them. Thus the lives of many of the little animals were spared without in any way lessening the value of the work from a sanitary point of view. It is only fair to say that farmers probably would have been much better satisfied had we not intervened in behalf of the little nuisances that are so destructive to certain crops.

Another field of usefulness of animal experimentation in relation to plague is illustrated by the following: In 1903, Simpson, a well-known student of the disease, made the assertion that the domestic animals and fowls found in Hong Kong, the meat of which was used for food, were susceptible to plague infection, and in his opinion constituted a possible source of danger. The determination of the facts in the case was obviously a matter of the greatest importance, and other workers took up the subject with the result that Simpson's findings were discredited¹³ and a source of confusion and error was eliminated. It would have been out of the question to disprove definitely the erroneous statements without recourse to animal experiments.

Another field of usefulness of animal investigation in relation to plague is the search for a biologic agent that will cause an epizootic among rodents that will exterminate these pests but will not harm human beings or useful domestic animals. Unfortunately, up to the present time nothing fulfilling the requirements has been found. The usefulness of such agents can be determined only by conducting feeding experiments with rats and other rodents. The layman is very likely to be misled by the glowing advertisements of the biologic products that are on the market, and if they are used on a large scale with unfavorable results, a false sense of security is engendered and money is wasted that could have been spent profitably in other ways.

In the consideration of the relation of animal experimentation to the plague question, one must never lose sight of the fact that large numbers of rodents suffer from the disease in nature, and it is certainly no exag-

geration to say that for each rat, guinea-pig or squirrel that has succumbed to the disease as a result of experimental inoculations, thousands of rodents have died of the same disease under natural conditions. The animal infected in the laboratory dies in peace and perhaps has his sufferings cut short by the merciful use of an anesthetic, while his brother infected in the ordinary course of events in nature is very apt to have his sufferings cut short only by the less merciful attentions of his cannibalistic comrades.

To follow to a logical conclusion the doctrine that animals should not suffer for the benefit of mankind would effectually put an end to the warfare against rodents; not only that conducted as a measure against disease, but as well that conducted by almost everyone on purely economic grounds. Traps and poisons are not merciful in their effects, and those who deplore the sacrifice of animal life made necessary by the advance of science would probably not hesitate to take measures looking to the destruction of the rat that has the pantry or the granary for the field of his activities.

PROPHYLAXIS AND TREATMENT

The matter of prophylactic measures that may be used to prevent plague infection or reduce the liability to it are clearly of great importance. The question of artificial immunization to plague is a subject that has received the attention of a number of observers. Haffkine's work along this line has given us a valuable weapon in the combating of plague. He injects killed cultures of the plague bacillus into persons with the object of creating a degree of immunity to the disease that would enable one to resist the invasion of the infecting organism. The method has been widely used in India and less extensively elsewhere. There is some difference of opinion as to the value of the procedure, but there is a very general agreement that no harm is done when the prophylactic is used with proper care. An unfortunate accident which occurred in connection with the use of Haffkine's prophylactic has materially interfered with its wider use. This accident was the infection of a number of persons with tetanus at the time of inoculation. The matter was made the subject of a rigid investigation and the evidence indicated that the tetanus was due to the accidental contamination of a vial of the

prophylactic while the latter was being prepared for use by a native assistant. Even had the accident been due to the improper preparation of the agent it simply would have pointed out the necessity for the utmost care in the manufacture of the prophylactic.

Haffkine and Bannerman¹⁴ in reviewing the work with Haffkine's prophylactic show clearly that there is a much reduced case incidence among the inoculated, and a startling reduction in the mortality of those in whom inoculation has failed to prevent infection. A particularly striking series of cases reported by Haffkine¹⁵ is that of a large series of numbered prisoners who were confined in a jail where plague prevailed. Those who bore even numbers were inoculated, while those having odd numbers were not inoculated. Among the uninoculated there occurred ten cases of plague, six of which were fatal; while among the inoculated there were three cases, all very mild and all of the patients recovered. Other series of almost equally striking cases might be cited. Forsyth,¹⁶ in an analysis of the figures of many thousands of cases, shows that the plague incidence among the inoculated was less than one-third of that among the uninoculated, while the mortality among those who had received the prophylactic was only 17 per cent.; and among those who had had no previous treatment it was 45 per cent. In other words, the chances of dying of plague were about eight times as great for those who had not received the prophylactic treatment. Numerous other reports of the same tenor might be adduced to demonstrate the value of the measure.

Strong¹⁷ advocates the use of living but attenuated cultures of the plague bacillus for the purpose of immunizing persons. This method has not been largely used, but the evidence that exists is in favor of the procedure.

The whole subject of artificial immunization has been developed in relation to plague as well as in relation to other diseases by means of experiments on lower animals, especially rats and guinea-pigs.

Now let us state very briefly what animal experimentation has enabled us to do for the person actually

14. Haffkine and Bannerman: Brit. Med. Jour., 1898, ii, 856.

15. Haffkine: Brit. Med. Jour., 1899, ii, 11.

16. Forsyth: Lancet, London, 1903, ii, 1646.

17. Strong: Philippine Jour. Sc., 1907, ii, 159.

stricken with the disease. In 1895 Yersin, Calmette and Borrel¹⁸ found that after animals were injected with killed cultures of the plague bacillus, the serum of the animals so treated acquired the power of preventing the development of plague in animals that were simultaneously infected, and in curing animals already sick. The serum for this purpose is now on the market as an article of commerce. It has been used in thousands of cases of the disease in all parts of the world. There is a general agreement of opinion that when administered in sufficient doses and sufficiently early in the disease, it constitutes a very efficient remedy. Unfortunately the cases are rarely diagnosed early enough to give the patient the full benefit of the serum. Chocksy¹⁹ says:

"Much depends on the early and free use of the serum. In patients injected on the first day or within a few hours of the onset of the symptoms one injection of 100 c.c. followed by another after six to eight hours and then if necessary by a third, after a similar interval would cut short the attack if the case be not pneumonic, malignant or septicemic."

There is very good reason for believing that with the exception of the use of the serum, treatment has scarcely any influence on the course of the infection.

Laboratory animals must be used in the preparation and the testing of prophylactics and the curative serum. No other method is available, and to prohibit animal experimentation would immediately and effectually stop all work and all progress along these lines as well as along other lines of investigation of plague.

CONCLUSION

To review briefly, we may say that in the past by means of animal experimentation there has been demonstrated the cause of plague, the means by which it is conveyed in nature from animal to animal, and from lower animals to man. At the present time we have effective means of controlling outbreaks of the disease, and of curing many of the sick. So much has been accomplished in the past that we may fairly hope that later investigations will still further extend our knowledge of the disease.

18. Yersin, Calmette and Borrel: Ann. de l'Inst. Pasteur, 1895, ix, 589.

19. Quoted by Strong, Philippine Jour. Sc., 1907, ii, 291.

If I might be permitted to suggest the lines along which we may expect progress they would be as follows:

1. The discovery of methods of rodent extermination more perfect than those we now have.
2. The development of a prophylactic agent that could be used without inconvenience on a large mass of the population.
3. The preparation of a curative serum, potent enough to make it useful even in late cases of the disease.
4. The discovery of a reliable method of early diagnosis of human cases without awaiting the results of culture and inoculation experiments. This will probably be in the nature of a test similar to the ocular reaction in typhoid fever or the cutaneous reaction in tuberculosis.
5. The circumstances governing the alterations of virulence of the bacillus.

All progress in the directions indicated will have to come about as a result of experimental work done on lower animals. Will any reasonable person say that this work must be stopped because it requires the sacrifice of even a large number of rodents? Shall the achievements of the past, splendid though they are, be the measure of what we shall know about this disease that claims so many victims and causes such enormous commercial losses? I believe that these questions may be left safely to the judgment of any unbiased person.



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MEDICAL CONTROL OF VIVISECTION

WALTER B. CANNON, A.M., M.D.

Chairman of the Council on Defense of Medical Research of
the American Medical Association

BOSTON

DEFENSE OF RESEARCH PAMPHLET XVI

Issued by the Council on Defense of Medical Research
of the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
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AMERICAN MEDICAL ASSOCIATION

535 Dearborn Avenue

Chicago, Illinois

MEDICAL CONTROL OF VIVISECTION *

WALTER B. CANNON, A.M., M.D.

Chairman of the Council on the Defense of Medical Research of
the American Medical Association

BOSTON

"A VILE pursuit," "a devilish science," "an organized system of barbarity"—this is medical research; "fiends," "demons," "human monsters"—these are the medical investigators; "torments" and "prolonged agonies"—such are the experiences of animals in the "torture-chambers" of the laboratories. Words to catch and hold rigid the ideas of men were never so industriously over-worked as these expressions. One who undertakes to read much of antivivisection writings is wearied not so much by the monotonous recurrence of the same old stories as by the constant attempt to horrify by epithets.

That these epithets have serious implications is not questioned by anybody; but whether the persons who use them so glibly are really proper judges, qualified by any instructive experience, may be questioned with very good reason. These persons have never entered the laboratories in which they declare animals are "cruelly tortured;" they have not seen the operations which they describe as "revolting." Their assertion that their inexperience is due to refusal of admission to the laboratories does not alter the fact of that inexperience. Nor is the refusal to admit them a confession that their charges are true. Any one of insight and judgement is never refused admission; but the opponents of research, untrained in biological studies and willing to sacrifice their fellow men to the comfort of laboratory animals, may reasonably be excluded, just as emotional persons are forbidden to witness an operation on a relative. The surgeon operating in the home does not permit of the "open door," yet he does not become thereby the object of

* Reprinted from the *North American Review*, June, 1910, by permission of the Editors.

malignant suspicion. And the confident opinions of an outsider, concerning the surgeon's work, would not gain credence merely because expressed with unqualified assurance.

As an example of the way in which opinions on laboratory procedures and laboratory workers become established, the story of a letter by Professor William James, widely published in the daily press last summer, is worth telling. Professor James wrote that he understood the defenders of vivisection to protest "*against any regulation whatever*" (italics original). "Their invariable contention, implied or expressed," he continued, "is that it is *no one's business* what happens to an animal, so long as the individual who is handling it can plead that to increase science is his aim." Later he declared that medical investigators, held together by powerful club opinion, deny every charge against them, concede no point of principle and sustain firmly "the preposterous claim that every 'scientist' has an unlimited right to vivisect, for the amount or mode of which no man, not even a colleague, can call him to account." Then, after disapproving of state inspection and after urging medical investigators to establish their own government, he affirmed that so long as they disclaim corporate responsibility and formulate no code of vivisectional ethics for laboratories to post up and enforce, "so long must the anti-vivisection agitation, with all its expensiveness, idiocy, bad temper, untruth and vexatiousness, continue." Professor James in his letter struck valiantly at both parties in the controversy. What a gift of ammunition he presented to the antivivisectionists! The assertions regarding the experiments—their waste of animal life, their subservance to club opinion, their failure to formulate a code for their own conduct, their sense of exemption from all restraint—these assertions they carefully selected, and they have since published them extensively and repeatedly, without question, as the words of final authority. Thus are the investigators judged, classified and stamped—with doctrinaire notions of what manner of men they must be and what lives they must lead, but with no suggestion of an inquiry whether perchance the assertions may not be true.

Nearly two years ago the American Medical Association appointed a Council to investigate the conditions of

animal experimentation in the medical laboratories of the United States. Through detailed reports and the testimony of an expert investigator the Council has accumulated information from every medical school in which animals are used for teaching or research. Some of the results of this inquiry should be of interest to the intelligent and humane persons to whom the antivivisectionist makes his appeal.

The experimental animals whose service for medical research rouses the greatest amount of hostile sentiment are the cat and the dog. The employment of these animals has been referred to as a terrible "waste" of life. Yet compared with the number of cats and dogs officially destroyed in various cities, the sacrifice of their lives in laboratories is almost insignificant. Figures have been obtained by the Council from twenty cities, in many of which, however, the record for cats was not reported; in these cities more than 360,000 cats and dogs have been killed in a single year merely to be rid of the excess. In New York City alone during the past fourteen years more than 800,000 cats and 400,000 dogs have been thus destroyed. In one year in New York City alone there are put to death more than ten times the total number of cats and dogs used for all purposes in all the laboratories in all the medical schools in the country. The interesting question now arises whether the enormous numbers of these animals killed solely to clear the streets have their lives "wasted" more or less than the much smaller number used in the laboratories for purposes of medical advancement.

But the humane destruction of animals in a public pound, antivivisectionists will declare, is very different from the "prolonged agonies" which animals experience in the "secret chambers" of the laboratories. Thus the habitual words assert their dominance. "Behind locked doors, where no one may enter," the "brutalized" experimenter, quite regardless of the "cries of pain and anguish" which assail his ears, is supposed to undertake his "hellish" work. "With unlimited right to vivisect, for the amount or mode of which no man, not even a colleague, can call him to account," he continues his "butchery." Before giving full credence to the implications of these charges against honorable men patiently searching out the nature of disease and its treatment, we

might do well to learn the actual conditions of research and the precautions taken by the medical profession itself to minimize suffering in laboratory animals.

In the largest medical laboratories of this country regulations governing animal experimentation have been posted and enforced, in one instance for more than thirty years, in other instances for more than ten years. These regulations, discovered by the Council of the American Medical Association, have been collected, summarized and revised, and have been sent to all other laboratories in which animal experimentation is conducted. These rules are as follows:

I. Vagrant dogs and cats brought to this Laboratory and purchased here shall be held at least as long as at the city pound, and shall be returned to their owners if claimed and identified.

II. Animals in the Laboratory shall receive every consideration for their bodily comfort; they shall be kindly treated, properly fed, and their surroundings kept in the best possible sanitary condition.

III. No operations on animals shall be made except with the sanction of the Director of the Laboratory, who holds himself responsible for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems.

IV. In any operation likely to cause greater discomfort than that attending anesthetization, the animal shall first be rendered incapable of perceiving pain and shall be maintained in that condition until the operation is ended.

Exceptions to this rule will be made by the Director alone and then only when anesthesia would defeat the object of the experiment. In such cases an anesthetic shall be used so far as possible and may be discontinued only so long as is absolutely essential for the necessary observations.

V. At the conclusion of the experiment the animal shall be killed painlessly.

Exceptions to this rule will be made only when continuance of the animal's life is necessary to determine the result of the experiment. In that case, the same aseptic precautions shall be observed during the operation and so far as possible the same care shall be taken to minimize discomforts during the convalescence as in a hospital for human beings.

Faculties of medical schools throughout the entire country have formally adopted the rules as an expression of the precautions under which research was being, and should continue to be, conducted. These or similar rules are now posted in practically all laboratories in which

animal experimentation is extensively practiced. The adoption of these rules effectively disposes of the charges that in laboratories "it is no one's business what happens to an animal," that experimenters protest against any regulation, and that they disclaim any corporate responsibility for their acts.

Power for the enforcement of the regulations is abundantly provided in the public and corporate manner in which they were adopted; and that power is reinforced by a strong "club opinion" to which the opponents of medical research have already recognized the experimenters as so perfectly loyal. Furthermore, the potent social forces expressed in the votes of the trustees of institutions, and in the opinions of colleagues and fellow workers, not to speak of the interested public, would put effective pressure on any tendency toward infraction of these regulations should such tendency develop. As a matter of fact, however, the members of the Council, who are widely acquainted with medical laboratories, are convinced that in the great majority of instances these regulations merely define the already good conditions under which experimental medicine has been carried on and state a program for the continuance of those conditions. To beginners in research and to interested people these regulations will indicate the spirit of the investigators and the consideration given by them to the avoidance of unnecessary pain.

Persons who have been under the spell of antivivisection phrases may perhaps now admit that in the laboratories of the great medical schools the condition of animal experimentation is fairly satisfactory. They will surely have the suggestion made to them, however, that there still remain the careless and inexperienced medical students who, in the secrecy of private rooms, are wholly free to satisfy their desire to operate on animals without any supervision whatever. What are the grounds for this suggestion? The uniform testimony given to the Council is that in the medical laboratories students are carefully supervised in any experiments they make on animals; indeed, except in a few places, they are not permitted to use any other animal than the frog. At most schools the students are carefully instructed in the great importance of the experimental method for the service of public health, and in the necessity of avoiding in every way the careless treatment of animals. At other schools

this precautionary instruction is regarded as superfluous—a view easily understood by any one who knows the character of young men studying medicine, and who realize the immense practical difficulties of private investigation. Until some respectable evidence is adduced to show that the much-maligned medical student actually does carelessly “cut up” living animals in his room, the evil suggestion that he does so should receive the contempt it deserves.

In spite of the accumulated evidence of a satisfactory condition of animal experimentation in this country, and in spite of the enforcement of the foregoing regulations in the laboratories, Professor James's intimations of peaceful subsidence of the agitation must be regarded as much too optimistic. No end to the struggle for legal interference with medical research is in sight. Every year in one state or another a “mild bill” will be alluringly presented. Its ostensible purpose, as in the past, will be not to prevent “legitimate vivisection” by responsible investigators, but to stop the practice among the unskilled—for example, the medical student in his room. Examination of the bill will reveal, however, that no provision is made for spying on the medical student in his room, but that every arrangement is made for the inspection of the responsible investigators. To many fair-minded people inspection of laboratories and laboratory-work seems highly reasonable; they approve of going at least so far with the petitioners for legislation. But the medical profession has in the main objected to the proposed inspection. What are the reasons for the objection?

In the first place, inspection of laboratories would not satisfy those who are eager for legislative interference with research. England has had laboratory inspection for thirty-four years, yet there is no country in which the attack on laboratory procedures is more relentless. No less than fifteen antivivisection societies afflict Great Britain, all opposed to medical progress through the use of animals. Furthermore, if we may judge by English experience, the inspectors must describe “horrors” or be discredited. Inspection in England has not revealed any noteworthy abuse of animal experimentation during all the thirty-four years. The inference drawn by the anti-vivisectionists is that occasional inspection is futile; indeed, that, unless an inspector is in the laboratories continuously during all operations, horrible abuse of

animals is sure to occur.¹ The impossibility of providing for such constant oversight would seem to a person of common sense to necessitate a certain amount of reliance on the good will and natural humanity of those engaged in research. Again, the argument for inspection, usually supported by analogy with bank inspection, is, under the circumstances, quite faulty. For the inspection of banks experts in banking are appointed, but for the inspection of laboratories experts in experimentation have been definitely excluded in the bills presented by the opponents of animal experimentation. For this important work they desire their own representatives. In the opinion of the experimenters, however, such persons, untrained in observing animal reactions and lacking any insight whatever into the extraordinary complexities of medical investigation, are thoroughly incompetent.

The incompetence of inspectors is the strongest objection to the proposal for state inspection. The laboratory workers have spent many years learning what is known of the vital changes in living organisms. They are busied with a study of the most perplexingly developed structures and the most involved and entangled processes in nature, the structures and processes in highly organized animals. And not only are the individual processes intricate, but animals and plants are intricately related in the nexus of living beings. The most gifted insight is required, and the rarest type of constructive imagination, to distinguish in this complex the relations that are important from those that are unimportant. Precisely this high order of ability is a prime requisite in the hard human struggle against disease. Work that seems remote and academic may have the utmost value for the welfare of mankind. Lister's revolutionizing of surgical methods began with a study of fermentation in flasks and went thence to experiments on animals. In the early days of Lister's work even the physicians had no eyes for his view. How much less could be expected of the ignorant inspector! Surely Professor James was correct when he wrote: "The fear of state rules and inspectors, on the part of the investigators, is, I think, well founded; they would probably mean either stupid interference or become a sham."

1. See Minutes of Evidence, English Parliamentary Commission on Vivisection, 1905-6, Coleridge's testimony, *passim*.

Occasionally, at relatively rare intervals, the solution of an important problem may require that animals shall suffer. There are antivivisectionists who declare that they themselves prefer to suffer rather than to profit by procedures involving pain to animals. The enormous majority of men, however, are quite willing to do otherwise. As a matter of course, society tolerates crushing of limbs in traps, or other grievous wounding of birds and beasts, merely for ornamentation or sport. Even the delights of the palate are served through the infliction of pain, for men gladly consent to eat the capon and the steer, the taste of whose flesh has been made more delicate by barnyard operations of the most shocking character. The lashing of dogs driven to the last extremity of fatigue and starvation has been required to carry the flag to the at last accessible pole. How much more justifiable than any of these purposes is the motive that impels the medical investigator! Indeed, how much more justifiable than any of these inflictions of pain is the occasional suffering caused in the laboratories—for is not "the life more than meat and the body more than raiment?" Men and women and children, whose suffering extends to every one bound to them by the strong ties of love and sympathy, daily go down to death because the disease is a mystery and its cure unknown. Who, then, shall say that medical research shall not continue to bring its blessings? In the eager search for more light, who shall decide the critical case involving pain to animals? The antivivisectionists maintain that they should decide; the medical profession, on the contrary, urges that the decision remain in its control. The antivivisectionists, unacquainted with the problems and methods of medical research, prefer to restrict their humanity to the welfare of laboratory animals. The medical profession, realizing that more power to fight disease can only come from more knowledge, trusts the deeper humanity of the laboratory workers who are seeking that knowledge. Should not the decision of the critical case rest preferably with the person of training and insight, the laboratory director? Of all men, he is most likely to know what is being done by those about him; he is most responsible to his institution, to his profession and to the public interest; and his position is itself a warrant of his trustworthiness.

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IMMUNOLOGY

A Medical Science Developed Through Animal
Experimentation

FREDERICK P. GAY, M.D.
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BERKELEY, CAL.

DEFENSE OF RESEARCH PAMPHLET XVII

Issued by the Council on Defense of Medical Research
of the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

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IMMUNOLOGY

**A MEDICAL SCIENCE DEVELOPED THROUGH ANIMAL
EXPERIMENTATION**

**FREDERICK P. GAY, M.D.
Professor of Pathology, University of California
BERKELEY, CAL.**



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Perhaps no other of the medical sciences can be so suitably discussed in relation to animal experimentation as immunology, because no other science has been so dependent on this method of attack for its development.

The science of immunity, or immunology, would explain the mechanism by which the animal body is enabled to resist disease. In addition to its fascination as a biologic science, immunology offers the added interest of the greatest human utility, the prevention and cure of disease; and precisely in this vital significance lies at once the importance of the science and a potential danger to its sound development. This danger arises in an overanxiousness to apply supposedly specific agents before the principles that underlie their apparent effect have been determined. The history of immunology has, indeed, brought into particular relief certain interesting relations of theory to practice, worthy of more philosophic discussion, but we may content ourselves with an attempt to point out the usual sequence of observed facts, logical deduction, inductive experiment, and, in concluded chapters, application of principle in the diagnosis and prevention of disease.

The relatively recent development of any exact knowledge of the mechanism of immunity is at first glance surprising, when we consider that certain examples of natural and of acquired resistance to disease have been recognized since ancient times. Some attempts to turn these recognized examples to practical use were from

the beginning successful, but none of them was inaugurated with that understanding of the principle involved which brings the greatest utilitarian reward. It is obviously no lack of human interest in the subject which has delayed the evolution of immunology, but largely the lack of a suitable method of attack on so obscure a subject. The method was eventually furnished by the recrudescence of the experimental idea as applied to medicine and particularly as exemplified in the progress that has been made in determining the causation of disease. Immunology, indeed, parallels bacteriology both in chronology and in method. Before considering the development of the experimental science of immunity we may outline:

I. THE DATA OF IMMUNITY ACQUIRED FROM CASUISTICS

The first and most wide-spread type of resistance to disease is the inborn or natural immunity which is evident on the initial exposure to a given malady. With an increasing intensity, as expressed in more and more marked resistance to infection, natural immunity serves to differentiate individuals of a given race, races of a given species, and species of animals from one another.

The individual type of natural immunity may be noted whenever a group is subjected to equal chances of infection or contagion; certain individuals succumb while others resist. A familiar example to illustrate this relative individual resistance is given in any group of pathologists who are performing numerous post-mortem examinations; some members of this group are veritable martyrs to post-mortem infections, whereas others are practically immune. This type of resistance is frequently temporary and in all respects relative; it is dependent on certain subtle differences in general health and nutrition and may be evidenced by certain changes in the bactericidal properties of the blood, to which reference will later be made.

Natural racial immunity, to which attention was called as early as the sixteenth century, is in all probability dependent on differences in food and general hygiene. It is difficult to be certain in many so-called examples of racial immunity that have been given whether the increased resistance is in reality inborn or simply acquired through recovery from disease. The marked resistance of certain races of mice to a transmissible

tumor (Haaland),¹ which resistance may actually be lowered by a change in environment, would seem a certain example of a natural racial immunity.

Species immunity is the most evident and distinctive type of natural immunity. The difference in resistance between any two species of animals to a given infection varies in general with the distance apart that these species lie in the animal scale. Although familiar examples of species immunity occur throughout the animal kingdom, those of the greatest interest occur in relation to a whole series of typical human diseases, syphilis, measles, typhoid fever, gonorrhea and the like, which never occur spontaneously in the lower animals, and cannot be transmitted to them or at best in modified form only. Recent studies with the higher anthropoid apes, however, have shown that at least certain of these typically human diseases (*e. g.*, syphilis and typhoid fever) may be produced in these animals because they are most nearly related to the human species. In a general way, species resistance may be attributed to differences in metabolism, body temperature, intestinal enzymes and the like.

Of far greater significance and practical bearing are those instances of immunity acquired through recovery from a given disease. It is a matter of human experience that man has usually but a single attack of many of the diseases to which he is peculiarly susceptible, such as smallpox, typhoid fever, measles and yellow fever. In the face of epidemics where only those that have been previously affected are spared it is evident that such recovered individuals are protected, not as the result of chance, but owing to some induced mechanism of protection against the disease. Similar conditions of acquired immunity have frequently been noted in domestic animals.

Logical deduction from these observed instances of acquired immunity long since led to attempts to reproduce this advantageous condition artificially. Empirical efforts have been made even among primitive peoples to induce in individuals some endurable form of a fatal disease so that they might subsequently be better protected from chance infection. The African Vatuas²

1. Haaland: Beobachtungen über natürliche Geschwülstresistenz bei Mäusen, Berl. klin. Wchnschr., 1907, xliv, 713.

2. Metchnikoff: L'Immunité dans les maladies infectieuses, Masson et Cie, Paris.

have been reported as practicing an efficient form of self-immunization against snake venom; the Moors early protected their cattle from pleuropneumonia by running under their skin a knife that had been plunged into the lung of an animal that had died of the disease. It is well known that the Chinese and other peoples of the East protected themselves from smallpox by variolation, which was effected by inserting the scabs of human smallpox lesions in the nose of healthy individuals. A similar method was introduced into England by Lady Mary Wortley Montague in 1721 and was employed until the observations of Jenner on the relation of cowpox to smallpox in 1798 led to the present method of prevention of the disease by vaccination. The chance that a disease of cattle (vaccinia) is intimately related to a fatal human disease and that an attack of the one in the form of a localized disease would protect against the more generalized malady, alone rendered Jenner's observation fruitful. No generalized conception of the principle of "vaccination with a virus of diminished virulence," as later established by Pasteur, however, existed. This is evidenced by disastrous attempts that were later made to prevent measles, diphtheria and scarlatina by similar methods.

II. THE DEVELOPMENT OF IMMUNOLOGY THROUGH ANIMAL EXPERIMENTATION

Centuries of careful observation of facts obtruded by Nature in the course of devastating epidemics had taught at least two important principles in regard to resistance to disease: an acquired immunity follows recovery from an attack in perhaps the majority of acute diseases; and in at least one instance (smallpox) this acquired immunity may be artificially induced through a mild form of the disease. In the past thirty years the assets of utility from our knowledge of immunity have been multiplied to an extent that it would be difficult to estimate, to say nothing of the additional data of present theoretical interest which may ultimately be available in practice. And this advance has been rendered possible by animal experimentation.

It is the purpose of an experimental science to replace accident by design. A disease produced experimentally in animals offers innumerable advantages to one interested in its natural history; it offers the only method

of obtaining the significant stages of the disease in complete series for more minute examination. Only the interruption of an experimentally produced disease at successive periods in its course can afford exact information as to the method by which infection spreads and immunity is produced.

The discovery of the fundamental principles of bacteriology by Pasteur and Koch, the isolation and cultivation of bacteria in pure culture, and the proved etiologic relation of a definite micro-organism to a given disease, gave new impetus to the principle of vaccination exploited by Jenner. The work of Pasteur and his pupils with the bacillus of chicken cholera on animals laid the foundation for the discovery of the great principle of vaccination by means of bacterial cultures of diminished virulence. This diminution of virulence was obtained, in the case of chicken cholera, by long growth on artificial culture media, and later, in the case of anthrax by subjecting the cultures to growth at high temperatures. Similar methods of vaccination have been employed in the case of swine erysipelas and blackleg. In all instances the method has been arrived at by careful experimentation on animals and the products now used broadcast in actual prevention are first tested for virulence on laboratory animals. It is not my purpose to enter into a discussion of the practical results of protective inoculation but simply to indicate how the method of animal experimentation in bacteriology enriched the data of immunity.

Immunology may be regarded as having been differentiated into a specialized science from the moment that effective attempts to explain the physiologic mechanism that protects immunized animals were made. Theories of immunity were offered by Pasteur, Koch and others, but they were based largely on speculation drawn from the bare results of infection rather than from experiments designed to expose the process of immunity itself. In 1876 Koch³ attributed conditions of immunity to some change in the condition of the blood. Pasteur's exhaustion theory (1880)⁴ supposed that bacteria fail

3. Koch: Cohn's Beiträge zur Biologie der Pflanzen, 1876, II, 300.

4. Pasteur: Compt. rend. Acad. d. sc., 1880, xc, 247.

to grow in immunized animals owing to a lack of proper nutritive substances. A similar condition could be produced in artificial culture media as was shown by the failure of fresh chicken cholera bacilli to grow in filtered media that had already served for the growth of this bacterium; the addition of a little fresh bouillon containing fresh nutritive substances permitted growth to proceed. Chauveau⁵ in the same year would have explained immunity as due to the retention in the body of certain substances which inhibit bacterial growth. It is of interest to note that in none of these theories is any allowance made for active participation on the part of the animal itself in the production of resistance. The theories of Nägeli, of Buchner and of Grawitz do at least emphasize a reaction on the part of the animal itself, although they have proved in other ways inadequate.

It remained for Metchnikoff, a biologist, to give the first experimental evidence explanatory of the process of immunity. In 1882 Metchnikoff began recording his observations on the function of the white blood corpuscles in protecting the body from disease, observations which in his hands and in those of his followers have continued fruitful to the present day. Mention had already been made before Metchnikoff of the presence and of the disintegration of bacteria within leukocytes and Panum⁶ in 1874 had even suggested that such cells might be serving some protective purpose. The general conception of the accumulation of leukocytes which characterizes inflammation, however, was that it was a means of spreading rather than of checking infection. Metchnikoff had been making studies of the origin of digestive functions in cells of mesodermal origin. He suggested that the inclusion of particles and cells within leukocytes was due to an active digestive function in these mesodermal cells and ventured the assertion that their diapedesis during inflammation was a protective mechanism. In one of the crustaceans, *Daphnia*, which frequently suffers from an infection with a form of blastomycete (*Monosporon bicuspidata*), Metchnikoff was able to show that the outcome of the

5. Chauveau: Compt. rend. Acad. d. sc., 1880, xci, 536.
6. Panum: Virchow's Arch. path.-anat., 1874, ix, 347.

infection depends entirely on the completeness with which the blastomyces is engulfed by the leukocytes of the host. He was soon after able to demonstrate that frogs and mammals also combat experimental bacterial infection by a similar process of phagocytosis.⁷

NATURAL IMMUNITY FROM BACTERIA

Although this phagocytic theory of immunity met at first with extreme opposition, its opponents have gradually yielded more and more toward complete acceptance of the interpretation that Metchnikoff has with persistence yet remarkable fairness of judgment insisted on. It is generally admitted that many forms of natural immunity in particular are best explained on a simple phagocytic basis. The more complicated types of acquired immunity are less directly, though unmistakably, related with activity on the part of the white blood-cells. Leaving until later a discussion of the part played in each form of immunity by the cells, we may briefly outline the mechanism of phagocytosis in those instances in which it has been shown to be distinctive.

In the first place, the phagocytic cells may be divided into two general types as regards function. The small, actively motile polymorphonuclear cells of the circulating blood are practically concerned only in making way with the bacteria which produce acute infections; these cells are called "microphages." Under "macrophages" are grouped the large mononuclear leukocytes and certain endothelial and fixed tissue cells; the function of these cells is to take up other animal cells, such as red blood-corpuscles and protozoa, and also certain bacteria, like the tubercle and leprosy bacillus, which produce chronic infections.

It has been shown by careful studies, both within the animal body and in mixtures made in the test-tube, that the phenomenon of phagocytosis may be divided into three phases. In the first phase the leukocytes approach non-virulent bacteria owing to a positive chemotactic influence which the latter exert. If the bacteria are markedly virulent, on the other hand, they exert a negative chemotactic influence. These important facts of

7. For detailed consideration of Metchnikoff's phagocytic theory, see Metchnikoff's *L'Immunité dans les maladies infectieuses*, which is also obtainable in English translation. (F. G. Binnie, Cambridge University Press.)

positive and negative chemotaxis were ingeniously demonstrated by Bordet⁸ who placed small capillary glass tubes filled with the bacteria to be tested in the peritoneal cavity of guinea-pigs and later measured the length of the columns of leukocytes that had penetrated the tubes. After reaching the bacteria the phagocytes engulf them, owing in all probability to an active ameboid process, although it has been suggested that this apparent activity is due in reality to a simple physical change of surface tension. The bacteria, once within the leukocytes, are broken up by a process of digestion. An extract of leukocytes may be made which contains an enzyme (cytase) capable of producing this digestion at body temperature outside the body and the extract has been shown to vary in accordance with whether it is derived from microphages or macrophages. The extract of microphages (microcytase) is particularly active against bacteria and is effective only in an alkaline medium; it has little effect on animal cells. Macrocytase, on the other hand, derived from the mononuclear cells, works best in an acid medium and destroys animal cells.

The active opposition with which Metchnikoff's cellular theory of immunity was at first met was directly productive of important facts which at first seemed to attribute the active protective power of the blood to the fluid portion rather than to the leukocytes. In 1885 Fodor⁹ showed that anthrax bacilli, when mixed with fresh rabbit blood in the process of clotting, were destroyed; and two years later Nuttall¹⁰ showed that fresh defibrinated blood would produce the same effect. In 1891 Buchner¹¹ proved this bactericidal effect of fresh blood to be due to the cell-free blood serum, whether it is obtained by defibrination or by clotting. Buchner further described certain ferment-like substances in the serum to which this destructive power over bacteria is due and to which he gave the name of alexins (from *ἀλέξειν* to ward off or protect). The alexins resist freezing and thawing, but are destroyed by heating to 55 C. for one-half hour. They are unaffected by dilution in physiologic salt solution and may be precipitated with

8. Bordet-Gay : Studies in Immunity, pp. 1 and 8. Wiley and Son
New York, 1909.

9. Fodor : Deutsch. med. Wchnschr., 1885, p. 435.

10. Nuttall : Ztschr. f. Hyg., 1888, iv, 353.

11. Buchner : Centralblatt f. Bakteriol., v, 817.

sodium sulphate. Such physical and chemical characteristics have caused alexins to be classed with the enzymes without any very profound knowledge as to their chemical composition.

Further studies, particularly those dealing with the origin of alexin, seem to have shown that the bactericidal property of cell-free serum is in reality no disproof of the correctness of Metchnikoff's conception of the cellular nature of natural immunity. There is good experimental evidence for the belief that the alexin of Buchner is never present in the blood plasma in the body, but is artificially liberated in blood serum by clotting, owing to a disintegration of the leukocytes which normally contain it. In other words, the "alexin" is synonymous with Metchnikoff's leukocytic ferment, the "cytase," which under usual conditions destroys bacteria within the cell (phagocytosis) and under abnormal conditions in shed blood is liberated in the serum. Many experimental observations have been adduced to prove this point. For instance it may be shown that the alexin varies with the degree of leucocytosis; leukocytic extract is essentially the same in its action as alexin; and alexin increases in the serum under conditions which favor disintegrating of leukocytes.

It would seem, then, that the leukocytes are largely responsible, either directly through phagocytosis or indirectly through liberation of cytase or alexin, for the condition of natural immunity from bacteria and animal cells. As we shall presently see, the study of conditions of acquired immunity, although in a measure complicating this explanation, has led to far greater insight of practical significance in combating disease.

IMMUNITY FROM TOXINS

At this point it is advisable both for reasons of chronology and exposition to interrupt temporarily our consideration of the mechanism of animal defense against bacteria as such. Bacteria that have gained entrance to the body are harmful, not only because they increase rapidly in numbers when unrestricted, but because they eliminate harmful products. These harmful products may be either simple chemical substances like acids and alkalies, bacterial proteins, known as ptomaines, or more particularly, in certain instances, true bacterial toxins. Toxins are albuminoid substances, of unknown chemical

constitution, which are specific both in their origin and in the effect they produce. They are endowed with certain other recognizable characteristics; they produce their harmful and specific effects only after a period of incubation; they are readily destroyed by heat; they act in very small doses; and lastly, as we shall presently see, they produce antitoxins. Pasteur, as early as 1880, noted that old bouillon cultures of the *Bacillus avisepticus* which had been filtered free from bacteria would, on injection into animals, produce symptoms of narcosis. In 1888 Roux and Yersin¹² described a toxin found in filtered cultures of the diphtheria bacillus which was fatal for guinea-pigs in very small doses. Although the possibility of specific protection from bacterial invasion by means of previous treatment with killed or modified bacterial cultures was then known, attempts at a similar protection against this diphtheria toxin were at first unsuccessful. In the following year Kitasato succeeded in obtaining a pure culture of the tetanus bacillus and in 1890 von Behring and Kitasato¹³ obtained tetanus toxin from such cultures. They found furthermore that by treatment with certain chemical substances the toxins of diphtheria and of tetanus could be weakened so as to be better supported by laboratory animals; animals treated with these weakened toxins became immune from doses of the whole toxin that were fatal to the normal animal. And, more important still, it was shown that the blood of such actively immunized animals would protect normal animals against subsequent injection of fatal doses of toxin, or would even cure, within reasonable time limits, animals that had already received the toxin. These experiments form the rational basis for the present highly effective antitoxin treatment of diphtheria and for the prevention of tetanus.

The interesting studies of Ehrlich¹⁴ as to the mode of interaction of antitoxin with toxin not only gave rise to an enormously ingenious and fruitful theory of immunity but determined the recognized method of estimating and standardizing, by the use of guinea-pigs, the exact curative value of diphtheria antitoxin. We need not concern ourselves with the theories of antitoxin effect,

12. Roux and Yersin: *Annales de l'Inst. Pasteur*, 1888, II, 629.

13. v. Behring and Kitasato: *Deutsch. med. Wchnschr.*, 1890, No. 49.

14. Ehrlich-Bolduan: *Collected Studies in Immunity*, ed. 2, p. 481, Wiley and Sons, New York.

as their interest, although of ultimate utilitarian value, is immediately largely academic. In addition to the better studied toxins of diphtheria and tetanus, true toxins have been described as formed by cholera vibrios, the bacillus of meat poisoning (*B. botulinus*), the dysentery bacillus of Shiga and the *Bacillus typhosus*. The exact relation of each of these latter toxins to pathogenesis of the disease in question is not fully determined nor can any final word be given as to the efficacy of an antitoxin treatment in many of these instances. In the case of the dysentery bacillus, at least, almost certain results may ultimately be expected from specific anti-toxin therapy.

ACQUIRED IMMUNITY FROM BACTERIA

Reference has already been made to the important discovery of Pasteur that animals could be immunized by means of cultures of diminished virulence. In 1886 Salmon and Smith¹⁷ showed that pigeons could be immunized against the hog cholera bacillus by means of cultures that had actually been killed by heat. In 1888 Richet and Hericourt¹⁸ proved that this antibacterial type of immunity is transferable from one animal species to another. Von Behring and Nissen¹⁹ demonstrated (1890) that the blood-serum of guinea-pigs that had been immunized against the *Vibrio metchnikovi*, would kill these micro-organisms better *in vitro* than would the serum of normal guinea-pigs.

The extreme interest that greeted the discovery of the antitoxins led at first to a misconception of the mechanism of the protection afforded animals by the inoculation of bacterial cultures. It was at once supposed that in the majority of instances, for example, in the immunity against spirilla, the protection was antitoxic. In 1894, however, Pfeiffer²⁰ began his studies with cholera infection and immunity which led to a revolution in our conception of acquired immunity from bacteria. Pfeiffer injected cholera spirilla into the peritoneal cavity of guinea-pigs that had been immunized by means of subcutaneous inoculations of this micro-organism. Whereas in the normal peritoneum the spir-

17. Salmon and Smith: Centralbl. f. Bakteriol., 1887, ii, 543.

18. Richet and Hericourt: Compt. rend. Acad. d. sc., 1888, cvii, 690.

19. v. Behring and Nissen: Ztschr. f. Hyg., 1890, viii, 412.

20. Pfeiffer: Ztschr. f. Hyg., 1894, xviii, 1.

illum increases rapidly in numbers and leads to a fatal infection, in the immunized peritoneum the vibrios are found to undergo rapid lysis; preparations made at intervals from the peritoneal exudate show increasing numbers of deep-staining granules which finally replace the normal vibrios entirely. Coincidentally with this "bacteriolysis" the animal recovers. Pfeiffer further showed that although his serum obtained from immunized guinea-pigs had in itself no destructive power for the vibrios *in vitro*, it would, when mixed with them and injected into the peritoneal cavity of normal guinea-pigs lead to the specific form of lysis.

Bordet²¹ was first to offer the correct explanation of "Pfeiffer's phenomenon," as it is called. He found that if the anticholera serum was employed soon after removal from an immunized guinea-pig it would suffice alone to destroy the vibrios in the test tube. Heating to 55 C. or conservation for several days destroyed this lytic property, but the property could be restored to the inactive cholera serum by the addition of fresh normal guinea-pig serum which in itself has no lytic property. In other words, the specific lytic effect of anticholera serum is due to the cooperation of two substances, one of which occurs in all fresh normal serums, is destroyed by heat, is non-specific and is identical with Buchner's alexin (Ehrlich's complement). The second substance, the *substance préventive* or *substance sensibilisatrice* (Ehrlich's amboceptor) as Bordet called it, is specific, occurs only as the result of immunization, and resists heating to 55 C.

The further investigation of the finer interaction of these two substances concerned in bacteriolysis was rendered possible by Bordet's discovery of the artificial hemolysins in 1898.²² Bordet found that the blood-serum of guinea-pigs that have received several injections of rabbit blood acquires the property of specific destruction of rabbit red blood-cells. He was further able to show that this corpuscle destruction or hemolysis is also brought about by the combined action of alexin with a specific sensitizer. These fundamental facts have since been amplified to an extraordinary extent by the

21. Bordet-Gay: *Studies in Immunity*, pp. 8 and 56.

22. Bordet-Gay: *Studies in Immunity*, p. 134 and subsequent chapters.

studies both of Bordet and of Ehrlich and his school.²³ Anti-hemolysins, composed in turn of antialexin and antisensitizer, have been described and their study has given great insight into the action of the antibodies in general. Ehrlich's explanation of the interaction of antibodies and their antigens has been on the line of organic chemical reactions, whereas Bordet has persistently favored an explanation in harmony with the laws of physical and later of colloidal chemistry. There is now little doubt that the colloidal theory best agrees with the facts.

Many other questions of at first academic and of later practical interest have arisen from the studies on bacteriolysins and hemolysins. Thus the dispute between Bordet and Ehrlich as to the unity or the multiplicity of alexins gave rise to Bordet's "reaction of fixation" which has served as a most valuable diagnostic test of bacterial infections and has been particularly exploited in Wassermann's test for syphilis. A study by Bordet and Gay²⁴ in refutation of Ehrlich's conception of the sensitizer as an amboceptor led to the conglutination reaction which promises much as a method of serum diagnosis.²⁵

As may well be conceived the explanation of acquired anti-infectious immunity on purely humoral lines is certainly suggested by the work of Pfeiffer, Bordet and Ehrlich and such explanation would seem to be in essential disagreement with Metchnikoff's phagocytic theory as applied to this type of immunity. The disagreement is, however, more apparent than real. Metchnikoff soon pointed out that Pfeiffer's phenomenon of extracellular bacteriolysis is exceptional and occurs practically only with such delicate micro-organisms as the vibrios. In even this instance Metchnikoff believes that the lysis is preceded by a destruction of leukocytes, which liberates the cytase or alexin from them into the surrounding fluid.

But even though it becomes generally accepted, as seems likely, that all alexin is derived from leukocytes the relation of Bordet's sensitizer to phagocytosis in acquired immunity remains to be explained. It is admitted that the sensitizer of immune serum is free even

23. Ehrlich-Bolduan: See *Collected Studies in Immunity*, ed. 2.

24. Bordet-Gay: *Studies in Immunity*, p. 363.

25. Gay and Lucas: *Proc. Soc. Exper. Biol. and Med.*, 1910, vii, 21.

in the plasma and in no sense an artificial product, as may be the case with alexin. The work of Denys and his pupils, which began in 1895,²⁶ threw the first light on this important question. Denys studied the protective and curative effect of an antistreptococcus serum on rabbits that had been infected with the streptococcus. He finds that the immunity afforded by this serum is due to its effect on the micro-organisms which renders them more readily taken up by phagocytes; the leukocytes themselves in the immunized animals do not differ from those of the normal animal. In 1902 Savtchenko²⁷ noted that a hemolytic serum likewise increases the susceptibility of the specific red blood-cells to phagocytosis. Neufeld and Rimpau²⁸ have followed the lead suggested by Denys and worked out with great care the effect of their "bacteriotropins," by which name they designate those substances in an immune serum which favor phagocytosis.

In 1903 A. E. Wright²⁹ described under the name of "opsonins" certain substances in the serum of human beings which when estimated quantitatively are supposed to indicate the intensity of the resistance of the individual to a given infection. Wright was able apparently to increase these protective opsonins, in case of lack, by "vaccination" with killed cultures of the micro-organism in question. Although Wright's work has the merit of attracting attention to the principle of cure by vaccination it is marred from a scientific standpoint by his failures to recognize the relation of his "opsonins" to the substances described by Denys, and particularly by the lack of fundamental experimental work on animals which subsequently in the hands of others has given us a more judicious attitude towards the theoretical and practical interest of his discovery. Animal experimentation has shown that even under the best experimental conditions, little value can be ascribed to Wright's "opsonic index" as an indication for specific treatment, grateful as such a method would be if accurate. Experimental work has further shown that the "immune opsonins" of Wright are probably identical with the "bacteriotropins" of Neufeld and Rimpau and probably differ

26. Denys and Leclef: *La cellule*, 1895.

27. Savtchenko: *Ann. de l'Inst. Pasteur*, 1902.

28. Neufeld and Rimpau: *Deutsche med. Wochenschr.*, 1904, and *Ztschr. f. Hyg.*, 1905.

29. Wright, Sir A. E.: *Studies in Immunization*, Constable, 1909.

quantitatively only from Wright's normal opsonins. Although Wright's first observations, which were not made under the best experimental conditions, led him to believe that his opsonins differed from the sensitizers of Bordet (Ehrlich's amboceptors) inasmuch as they are apparently thermolabile (55 C.), there now seems no reason for this artificial separation.

The following summary is, I believe, consistent with the facts at our disposal and is offered as a simple explanation of anti-infectious immunity. Bacteria are destroyed in the body of an immune animal by the action of two substances, the sensitizer which is the specific result of immunization, and which lies free in the plasma, and the alexin which under usual conditions in the body lies within the phagocyte. If phagocytosis has taken place the alexin works *in situ*; if phagolysis occurs the alexin is liberated and acts in the fluid extracellularly. There is, further, reason to believe that the more potent the sensitizer the more likely it is that phagolysis should occur, and in all events the greater the sensitization is the less the alexin required.

In vitro the bacteria are destroyed in a similar manner except that under such conditions when fresh serum is employed free alexin is the rule. When the alexin employed has been retained in the phagocyte as in the case in opsonin experiments, the destruction is intracellular subsequent to phagocytosis. The reason that normal opsonins are apparently thermolabile is because the normal extracellular alexin is destroyed and the normal opsonin (sensitizer) is not sufficiently potent to draw out the intracellular alexin or to cause the opsonized bacterium to be drawn within the cell. The destruction of the extracellular alexin is immaterial, however, in the case of immune opsonins (bacteriotropins) as their strong sensitizing power either makes use of a trace of alexin liberated by the phagocytes or else suffices to draw the treated bacteria within the cell.

The discovery of the artificial hemolysins gave rise to the hope that specific immune serums for other animal cells might be produced. The possibility of a specific epitheliolysin was particularly alluring in view of treatment of malignant tumors. The general conception of the cytolysins now is that they are specific for any cell of the species that has furnished the antigenic tissue rather than for any particular type of cell.

At this point may be mentioned certain other properties of immune serums that were discovered in connection with the studies on bacteriolysis and hemolysis. Charrin and Roger³⁰ noted as early as 1889 that a specific serum which was active against *B. pyocyanus* would clump cultures of this bacterium and the specific nature of this phenomenon of agglutination and many of the factors that control it were worked out by Bordet in 1895.³¹ The applicability of the agglutination reaction in the diagnosis of bacterial infections was exploited by Gruber and Durham in 1896.³² The early work of Kraus, 1897,³³ of Tschowitsch³⁴ and of Bordet, 1899³⁵ with bacteriolytic and hemolytic serum disclosed the specific phenomenon of precipitation which was soon applied in the well known forensic test for blood by Wassermann and by Uhlenhuth.

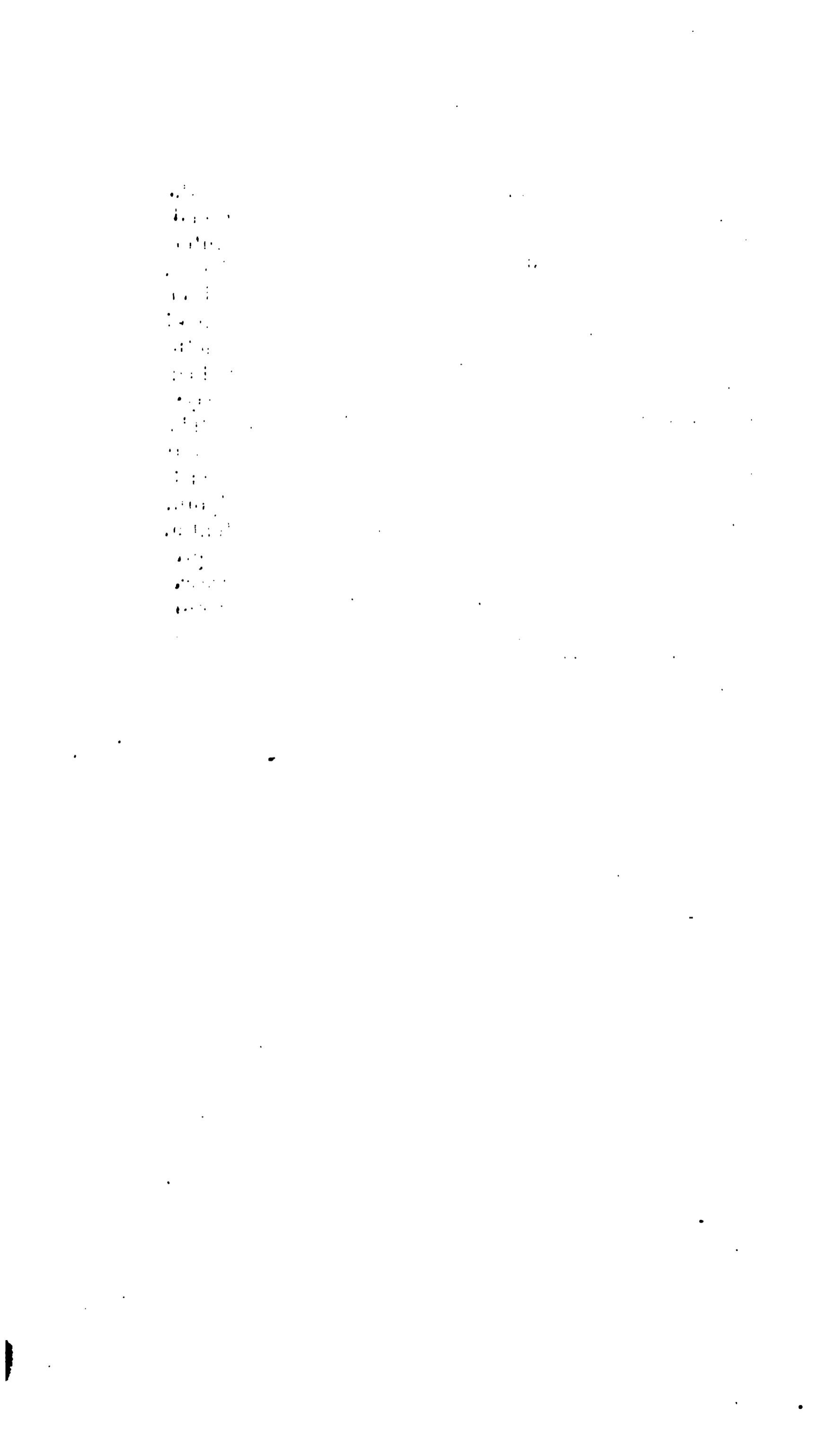
In concluding this outline of the development of immunology mention should be made of the interesting phenomenon of anaphylaxis or increased susceptibility, which under certain conditions follows injection of harmful proteins such as bacteria or of non-toxic proteins like horse serum. Rosenau and Anderson³⁶ and Otto³⁷ (1906) were first to draw attention to this condition, although it had been previously described and named by Richet. Rosenau and Anderson described the violent convulsive reaction, frequently followed by death, which follows the injection of horse serum in guinea-pigs that have previously received a minute dose of the same substance. Similar reactions have been studied following injections of bacteria. This extraordinary condition, which is apparently the opposite of the protective reactions of immunity, bears some mysterious but undoubtedly relation to the latter process. Although the outcome of the numerous studies on the relation of anaphylaxis to immunity now in progress are doubtful, little doubt may be entertained as to their theoretical interest and practical importance.

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- 30. Charrin and Roger: Compt. rend. Soc. de biol., 1889, p. 667.
 - 31. Bordet-Gay: Studies in Immunity, p. 142.
 - 32. Gruber and Durham: München. med. Wchnschr., 1896, p. 285.
 - 33. Kraus: Wien. klin. Wchnschr., 1897, No. 32.
 - 34. Tschowitsch: Ann. de l'Inst. Pasteur, 1899.
 - 35. Bordet-Gay: Studies in Immunity, p. 148.
 - 36. Rosenau and Anderson: Jour. Med. Research, 1906, xv, 179.
 - 37. Otto: Leuthold Gdnkschr., Berlin, 1906.

CONCLUSION

This article has attempted to outline step by step the development of immunology, a science worthy of specialized consideration both on account of its biological interest and its vital applicability. Nothing more than a suggestion of the application of immunology has been given. It has been evident that no true conception of the principles of immunity was possible until the methods of experimentation on living animals were applied. And each successive principle determined has of necessity depended on further animal experimentation. The sacrifice of animal life necessitated in acquiring our present knowledge of the mechanism of animal resistance to disease would seem justified from the standpoint of theory alone. In view of the present and potential value of applied immunology in the diagnosis, the prevention, and the cure of human and animal disease, skilled animal experimentation necessitates the encouragement of every humanitarian.

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Obstetrics and Animal Experimentation

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"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

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OBSTETRICS AND ANIMAL EXPERIMENTATION

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[EDITORIAL NOTE:—Dr. Williams is well fitted to speak on the above subject. He is one of the fourth generation of a family of physicians, who have been continuously engaged in the practice of medicine since 1770. He is dean of the Johns Hopkins Medical School and has been associated with it and the Johns Hopkins Hospital since its opening as assistant in gynecology, associate, associate professor and professor of obstetrics. He is a member of the Board of Charities of Baltimore City, a member of the Executive Committee of the Federated Charities, Baltimore, and holds membership in many prominent American and foreign obstetric and gynecologic societies. In connection with the work of the Board of Charities he has been especially interested in the hospital care of the sick poor of Baltimore, and has been instrumental in inaugurating the beginning of a well-equipped city hospital, which will be devoted to the care of the poor and to medical teaching.]

Unfortunately, the relation between animal experimentation and obstetrics appears at first sight to be less direct and striking than in many other branches of medicine. Nevertheless, I consider that it can be demonstrated beyond peradventure that the greater part of the advances made during the past thirty-five years have resulted either directly or indirectly from research of this character.

The chief advances in obstetrics, in which animal experimentation has played a part, may be summarized as follows:

1. The recognition of the bacterial origin of puerperal infection, which has enabled us to prevent and overcome its former terrible mortality.
2. The application of aseptic technic to various obstetrical operations, thereby rendering comparatively harmless many procedures which were formerly murderous.
3. The recognition of the bacterial nature of certain infectious diseases of the newly born child, such as lockjaw and umbilical infections, which enables us to save each year the lives of thousands of infants, which under former conditions would have been lost.
4. The biologic study and standardization of certain drugs, such as ergot, whereby efficient preparations are available for the prevention and control of hemorrhage.
5. The demonstration of the internal secretion of the ovary, which has led to the therapeutic employment of ovarian tissue extracts, and to greatly increased conservatism in operations on the ovaries.
6. Experimental studies concerning the nature of the toxemias of pregnancy.
7. The experimental production of fetal deformities, which has led to a clearer conception of teratology, and the abandonment of the superstitious belief in maternal impressions.

1. THE RECOGNITION OF THE BACTERIAL ORIGIN OF PUERPERAL FEVER

Those not familiar with the older obstetrical literature scarcely realize the extent of the ravages of puerperal infection before the introduction of rigid anti-septic precautions in the conduct of labor, as well as the almost miraculous revolution which has followed their employment.

In this connection, I shall attempt to give some idea of the mortality attending puerperal infection in the past, and of the confusion regarding its nature. Then I shall refer to the part played by animal experimentation in the development of the bacteriology of wound infection and the establishment of aseptic technic, as well as the demonstration of the bacterial nature of puerperal infection, and finally I shall refer briefly to the revolutionary results which have followed the practical application of these principles.

In preantiseptic times puerperal fever ravaged the lying-in hospitals throughout the world, and each year caused the unnecessary death of thousands of women in the best years of life. How great the mortality was

can best be appreciated by referring to the results obtained in the various civilized countries of the world, prior to the recognition of the etiologic rôle of the streptococcus.

PUERPERAL FEVER IN FRANCE

LeFort, in his railing accusation against the lying-in hospitals of France, which appeared in 1866, calculated that 30,394 deaths from puerperal fever had occurred in the 888,312 women delivered in the hospitals of Paris up to the year 1864—an incidence of 3.5 per cent., or one death to every 27.2 labors. Moreover, he stated that from 1860 to 1864, inclusive, the mortality in the Maternité of Paris was 12.4 per cent., which in December, 1864, rose to the colossal height of 57 per cent.; while in the Clinique it averaged 14.7 per cent. between the years 1833 and 1864, and on several occasions rose above 20 per cent. On the other hand, the mortality outside of the hospitals was much less, as only one woman perished out of every 212, which indicated that seven-eighths of the hospital deaths were due to conditions prevailing in them.

Such results were not limited to the past century, as Tenon in 1788 reported that the mortality at the Hôtel-Dieu for the fifteen years prior to 1786 was 6.4 per cent., and described almost inconceivable conditions of over-crowding and filth. Other observers described similar conditions. Thus, Charrier recorded a mortality of 7.5 per cent. at the Maternité in 1854, and Depaul one of 5.3 per cent. at the Clinique in 1856. Tarnier in his graduation thesis pointed out that 114 deaths from puerperal fever had occurred at the Maternité during the year 1856, an incidence of 5.1 per cent., as compared with 0.31 per cent. in the portion of the city immediately adjoining it.

Malgaine likewise studied the results in 14,197 and 99,911 women delivered respectively, in the hospitals and in the city of Paris during the years 1861 and 1862, and found a mortality of 8.2 and 0.56 per cent.; while Quinquaud stated that 65 per cent. of all women delivered in the St. Antoine Hospital during the year 1869 were infected. Moreover, Delaunay in his recent history of the Maternité de Paris reports that the average mortality for the ten years ending with 1869 was 10.12 per cent., which rose as high as 18.43 per cent. in 1864.

Naturally, such results could not pass unnoticed, and the subject was frequently brought up for discussion. Thus, following a paper on puerperal fever by Guérard before the Académie de Médecine in 1858, a discussion arose which lasted for five months, which led to no definite conclusions, although participated in by the leading authorities in France. Similar discussions also occurred before the Académie in 1861 and 1862, the Société de Chirurgie in 1866, and the Société médicale des hôpitaux in 1869 and 1870. In all of them the most divergent views were expressed, some speakers holding that puerperal fever was contagious, and others that it was an unavoidable visitation of Providence. All sorts of theories were advanced in explanation of its origin, and it was attributed in turn to the peculiar characteristics of the parturient and puerperal woman, to hospital miasms and to the filthiness, faulty construction and ventilation of the hospitals, but not a word was said concerning the dirty hands of the obstetrician. Every suggestion was tested as soon as made, but still the mortality continued unchecked. Finally, in desperation it was suggested that the old lying-in hospitals be abandoned and be replaced by smaller ones, accommodating only a limited number of women, and that most women be cared for in their own homes or in small institutions conducted by specially appointed midwives. At the end of this period, the results had become so intolerable that it became the prevailing opinion that epidemics could be combated only by closing the lying-in hospitals, and such a drastic remedy was forcefully recommended at the International Congress held at Brussels in 1875.

The prevalence of puerperal fever had become a scandal, and, passing beyond purely medical circles, engaged the earnest attention of the Bureau of Public Assistance, whose able director, Husson, after thoroughly investigating the subject, was forced to admit that he saw no way of coping with it, and said:

For the past sixty years the combined efforts of the administration and of the chiefs of service of health, have not been able to control the curse of puerperal fever, and up to this time the only palliative means of any effect in opposing the evil has been the momentary evacuation of the infected wards. The figures received from the various services of obstetrics still show a mortality high enough to call forth investigation, and to engage the friends of science and humanity to search

in every possible way by what means it may be possible to arrest the progress of so terrible a malady, which up to the present time has disappointed all calculations.

It is interesting to note that the monumental work of LeFort, whose statistics are quoted above, was undertaken at the instigation of Husson; but, when the report was ready and showed so clearly the glaring conditions in France, the Bureau of Public Assistance would not allow it to be published under its auspices. The following quotation from Hervieux's immense work on puerperal infection, which appeared in 1870, will also serve to indicate the gravity of the situation:

The puerperal epidemics are to woman what war is to man. Like war they destroy the most healthy, the bravest and the most useful portion of the population; like war they take subjects in the flower of their age and spread terror and desolation throughout the territory which they devastate. It belongs to politics to preserve us from the calamities of war, but to medicine is reserved the task of preventing and doing away with such epidemics.

PUERPERAL FEVER IN GERMANY

Conditions similar to those in France likewise obtained in Germany, but owing to the smaller size of its lying-in hospitals, the epidemics were usually not so extensive. Hirsch, in his handbook of historical-geographical pathology, stated that the death-rate in lying-in hospitals varied from 2 to 4 per cent.; while Winckel, on the basis of 701,322 labors in hospitals and 381,855 in private practice, calculated that the average mortality was 3.4 and 0.6 per cent. respectively.

On behalf of the Berlin Obstetrical Society, Boehr in 1877 undertook to study the mortality from puerperal fever in Prussia, and found that in the sixty years ending with 1875 the appalling number of 363,624 women had died from it in that state alone. Moreover, he calculated that the disease was the cause of 12 per cent. of the total number of deaths occurring in both sexes between the ages 15 and 50 years which increased to 18.58 per cent. between the ages 25 and 30 years. Furthermore, assuming that each marriage would result in 4.2 children, he estimated that every thirtieth married woman in Prussia would eventually fall a victim to it.

Based on Boehr's work, and its own investigations, a committee of the society presented a *Denkschrift* to the

minister of education, in which it was stated that many more persons died from puerperal fever than from cholera and small-pox combined, although sixteen epidemics of the former disease had occurred during the period covered by the statistics. For the protection of the public health, it was urged that the disease be made a "notifiable" one, so that steps could be taken to regulate the practice of midwives. Hegar made a similar study of the conditions in Baden and found that 0.732 per cent. of all labors ended fatally, one-half of the total number of deaths being due to puerperal fever.

While such results were bad, they did not compare with the conditions prevailing in the lying-in hospitals. Busch and Seyfert reported a mortality of 2.58 per cent. and of 3.5 per cent. in the clinics of Berlin and Prague, respectively. Carl Braun stated that in 98,902 deliveries in the Vienna clinic, between the years 1839 and 1853, the mortality was 4.6 per cent., which even in the pay department reached 2.9 per cent. Ahlfeld relates that during the year in which he served as intern in the Leipzig clinic, 5 per cent. of the women died from puerperal fever and 47.3 per cent. were seriously sick.

Similar results might be adduced more or less indefinitely, but it will suffice to mention that Feige recorded a mortality of 13 per cent. in the Charité in Berlin in 1861 and 1862. Olshausen one of 3.3 per cent. in Halle for the years 1871-1875, and Hecker one of 1.3 per cent. in Munich for the twenty years ending 1879. The work of Boehr was continued by Ehlers in 1900, who found as the result of aseptic precautions that the mortality in the large cities had been reduced by one-half, but had remained practically unchanged in the country districts.

PUERPERAL FEVER IN GREAT BRITAIN

Epidemics of puerperal fever were reported in the eighteenth century by Hunter, Denman, Hulme, Leake, Kirkland, Clarke, White, Gordon and others, the most extensive being that recorded by White in the Lying-In Hospital of Manchester, where the mortality was 4.1 per cent. between the years 1755 and 1771. Owing to the comparatively small size of the lying-in hospitals of Great Britain, and particularly to the early recognition by English physicians of the contagious nature of puerperal fever and its relation to erysipelas, the epidemics were not so extensive and were less fatal than those on

the continent; nevertheless, prior to the antiseptic period the results obtained were very discouraging. Until recently, the Rotunda Hospital in Dublin was the only large lying-in institution in the British Empire, and its results have been recorded by Churchill, Kennedy and Steele. The latter stated that in 198,481 labors, occurring up to the year 1870 the average mortality was 1.39 per cent., which rose to 3.27 per cent. between 1861 and 1870. He also reported that for the twenty-two years preceding and including 1876, the several London lying-in hospitals presented the following mortalities:

	Per cent.
Queen Charlotte Hospital	2.82
British Lying-In Hospital.....	1.57
General Lying-In Hospital.....	1.41
City of London Lying-In Hospital.....	1.35

According to Bristowe and Holmes the mortality in the York Road Hospital for the twenty-four years ending with 1858 was 2.9 per cent., which rose to 26.7 per cent. during the epidemic in 1838; while Florence Nightingale stated that between 1862 and 1865 the mortality in the Kings College lying-in department was 3.3 per cent. and was considered so serious that the service was discontinued.

Some idea of the seriousness with which the condition was regarded was shown by the appearance of an editorial in the *Lancet*, only a few weeks after the appearance of Lister's first article on antiseptic surgery, recommending the closing of all lying-in hospitals. Moreover, Kennedy in 1869 advocated evacuating the Rotunda Hospital in Dublin and delivering the women in tents or shacks scattered throughout its grounds; while Florence Nightingale considered that large lying-in hospitals could never be conducted safely and that their employment for the training of students was incompatible with a low death-rate.

Following a paper by Spencer Wells, the entire question of puerperal infection was thoroughly discussed before the London Obstetrical Society in 1875. All of the prominent obstetricians of the time took part in the discussion, and, while the most divergent views were expressed concerning its nature, the general consensus of opinion was that lying-in hospitals had an inherent mortality which could probably never be overcome.

This feeling is well illustrated by the following quotation from Barnes:

There is only one secret of safety, and that is to have the woman confined at her own house where she can have her own nurse, who has not been anywhere in the way of infection, and her own medical man who is free from infection. Then the chances are that she will come on favorably and happy. Without that there is no security. The lying-in hospital is not now by any means so serious a matter as it used to be; still it is always like sitting on a volcano; it may explode at any moment.

Furthermore, the general feeling of helplessness was well expressed by Duncan, in his monograph on "The Mortality of Childbed," when he said:

The disease may have its ravages restricted, but it is yet to be shown that it can be altogether prevented. It is in truth as little preventable as any disease in the nosology, or any crime in the statute-book. It is possibly preventable, but it has certainly never been prevented.

Even after the introduction of antiseptic methods, the views as to the undesirability of lying-in hospitals continued to persist in England; and as late as 1885 one of the sections in Playfair's text-book on midwifery was entitled "Should Lying-In Hospitals Be Abolished?" Indeed, the improvement in that country has been less marked than elsewhere, as Cullingworth, after studying the statistics of the Registrar General's office for 1897, stated that the general mortality had shown no decrease, except as compared with the year 1843; while Boxall reported a similar condition of affairs as late as 1905.

PUERPERAL FEVER IN THE UNITED STATES

That the United States was not spared in this regard is shown by the fact that Hodge reported a mortality of 5.6 per cent. in the Pennsylvania Hospital for the thirty years preceding 1833. Lusk observed an epidemic in the Bellevue Hospital in 1872 with a mortality of 18 per cent., which led to the removal of the department to Blackwell's Island. But even there the infection continued until after the introduction of antiseptic methods. Similar results were observed in the New York Maternity Hospital, where Garrigues noted a mortality of 4.17 per cent. for the years 1875-

1883, which in the latter year, just prior to the introduction of antiseptic methods, rose to 7.17 per cent.

PUERPERAL FEVER IN SCANDINAVIA

Even Scandinavia was not spared, and Stadfeldt reported the following results from the Copenhagen lying-in hospital: 1822-1843, 5.3 per cent.; 1850-1864, 4.1 per cent.; 1865-1874, 2 per cent. Similar conditions prevailed in Stockholm, and according to Netzel the average mortality was 4.5 per cent. in 45,863 labors occurring in the lying-in hospital during the 102 years ending 1877, and in four years it rose as high as 13 per cent.

VIEWS CONCERNING THE NATURE OF PUERPERAL FEVER

Sedillot stated in 1817 that puerperal fever was not a distinct disease, but rather an ordinary infection, which was modified by the puerperal state. It required, however, nearly seventy years before this doctrine became generally accepted.

The infectious nature of puerperal fever was first clearly emphasized by Gordon of Aberdeen, who based his conviction on seventy-seven cases observed during an epidemic in Aberdeen between the years 1789 and 1792. Among other things, in his forceful monograph, he wrote:

"It is a disagreeable declaration for me to mention that I myself was the means of carrying the infection to a great number of women"; and, in another place, "Fresh air and cleanliness are not sufficient for the destruction of the contagion, which can only be effected by fire and smoke."

Notwithstanding these clear-cut teachings, and the conclusive evidence which Gordon adduced in their support, the medical world was but little affected, and it was not until after the introduction of Listerian methods that such ideas became generally accepted. Similar views were forcibly and eloquently expressed in 1843 by Oliver Wendell Holmes in his monograph on "The Contagiousness of Puerperal Fever," which was reprinted with additions in 1855 under the title "Puerperal Fever as a Private Pestilence." His teachings, however, were opposed by Hodge and Meigs, the leading obstetricians of the day, and, while impressing many practitioners with the necessity of temporarily

abstaining from obstetric work when several fever cases had occurred in their practice, they had no effect on the results obtained in lying-in hospitals. Kneeland expressed similar views in 1847, which met with the same fate.

The most important contribution to this aspect of the subject was made by Semmelweis in 1847, who, after carefully studying the causes underlying the horrible mortality in the lying-in hospital of Vienna, came to the conclusion that the disease was identical with wound infection, and was due to the contamination of patients by hands soiled by contact with autopsy material or wound secretions. Furthermore, he thought that its propagation could be checked by washing the hands in a solution of chlorinated lime, by which means he was able to reduce the mortality from 11.4 to 1.27 per cent.

Semmelweis' views concerning the nature and causation of puerperal fever were perfectly clear; and if, in the following quotation, one substitutes the words "pyogenic bacteria" for "decomposed animal organic material" his conception holds perfectly good at the present time. After stating that he regarded child-bed fever as a resorption fever, he continued:

The decomposed animal organic material, which when absorbed causes child-bed fever, is in the vast majority of cases brought to the individual from without. These are the cases which represent child-bed fever epidemics, and these are the cases which can be prevented. The carrier of the decomposed animal organic material is the examining finger, the operating hand, bed-clothes, the atmospheric air, sponges, the hands of midwives and nurses which have been in contact with the excreta of seriously sick puerperal women or other ill persons and then handle parturient or recently delivered women. In a word, the carrier of the decomposed animal organic material is anything which has been contaminated by decomposed animal organic material and then comes in contact with the genitals of the individual. The area from which the decomposed animal organic material is absorbed is the internal surface of the uterus, extending upward from the internal os. As the result of pregnancy this has been robbed of its mucous membrane, and accordingly presents a surface which is unusually adapted for absorption.

His original observations were brought to the attention of the profession by Hebra in 1847, while his entire doctrine was laid down in his book, "Die Aetiologie,

der Begriff und die Prophylaxis des Kindbettfiebers," which appeared in 1861. In spite of his clear-cut views, his teachings were opposed by the leading authorities of Germany and France, and he died a disappointed man. He nevertheless prophesied that his views would eventually be universally accepted, and, in a postscript to his great work, wrote:

But should it not be vouchsafed me, which I hope God may prevent, to see this happy time with my own eyes, nevertheless the conviction that such a time must inevitably come sooner or later will cheer me in my dying hour.

Almost simultaneously with Semmelweis, Simpson insisted on the contagious nature of the disease and its identity with ordinary wound infection. More or less similar views were also expressed by Tarnier in 1856 and by Troussseau in 1858; but it was necessary for many years to elapse before they were accepted by the general mass of the profession.

The discrepancy of opinion on the subject is well illustrated in connection with the proposal to erect a new lying-in hospital in Prague, when the Bohemian Landtag submitted to a commission composed of Oppolzer, Rokitansky, Skoda, Virchow, Lange, Schwarz, Hecker and Loeschner, a series of questions concerning the contagiousness of puerperal fever and the advisability of replacing large lying-in hospitals by small ones. Without hesitation, the first three members of the commission replied that the disease was infectious and its spread could be prevented by proper precautions; whereas, the remaining members held various views, but all agreed that large lying-in hospitals were highly dangerous and that the disease could be combated only by greatly limiting the number of women cared for in such institutions.

A similar divergence of opinion continued until after 1875, when the discoveries of Lister and the bacterial origin of puerperal fever first began to be accepted. Prior to that time, the condition was generally considered as unavoidable, and was attributed to cosmic, atmospheric or telluric influences, to the genius epidemicus, imperfect ventilation and all sorts of other conditions; but, with the exception of a few far-seeing men, no one believed that it could be communicated from one patient to another by means of a dirty finger.

The teachings of Lister were introduced into France in 1875 by Championnière and Budin, and were popularized in Germany by a personal tour. Ahlfeld has given an interesting reminiscence of Lister's visit to Leipsic at that time, and has preserved a verse sung in his honor.

Just sind es jetzt fünf Jahre her,
Da drang die Kunde übers Meer ;
Es lebt ein Mann in Edinburg,
Das sei ein eigener Chirurg,
In Karbolnebel eingehüllt,
Der rings die Luft mit Dünsten füllt,
Betriebe er mit aller Macht,
Die niedere Bakterienjagd . . .

Prior to that time only a few voices were raised in support of the bacterial nature of puerperal fever, and Lee and Sir Spencer Wells were practically alone in England in advocating it. Indeed, such views did not begin to receive general acceptance until after Pasteur had cultivated the streptococcus and demonstrated it before the Académie de Médecine de Paris, in March, 1879.

It is interesting to recall the fact that the demonstration was preceded by a paper by Hervieux, in which he said:

“I lay down the principle that the inferior organisms as yet known, vibrions, bacteria, batonnets and moving bodies, cannot possibly explain the production of puerperal septicemia,” and concluded, “but I must confess that I have a terrible fear, a fear from which I am not able to rid myself, and which the academy will understand; and that is that I shall die before any one will have discovered that vibron.”

Immediately afterwards Pasteur arose and drew on the blackboard several chains of little dots, which he stated he had every reason to believe were its actual cause. This was the beginning, but many years of persistent investigation were required before the bacterial nature of puerperal infection was universally recognized, and, even as late as 1886, Credé in Germany and Munde in this country were doubtful whether sufficient proof had been adduced in its support.

THE DEVELOPMENT OF BACTERIOLOGY; AND RECOGNITION OF BACTERIAL ORIGIN OF PUEPERAL INFECTION

This is not the place to trace the history of the development of bacteriology in general, or even its applica-

tion to wound infection. As far as I can learn, the relation of bacteria to infectious diseases, and the necessity of recourse to animal experimentation for its demonstration, was first clearly expressed by Henle in 1840. He prophesied that the "contagium" in infectious diseases must be a living organism, and laid down the following criteria, which must be fulfilled in order to prove such a relationship:

1. The constant presence of one and the same microorganism.
2. Its isolation.
3. The experimental study of the same by animal experimentation.

Following this, the development of bacteriology as applied to medicine was comparatively slow, and it was not until after the work of Pasteur on putrefaction, and the application of his ideas to surgery by Lister, that very considerable advances were made. Indeed, it may be said that extensive development along these lines was not possible until after Koch, by the discovery of solid culture media, had put into our hands a convenient method of isolating and cultivating bacteria. Almost immediately following this invention, the various bacteria concerned in ordinary wound infection were isolated and their pathogenic action demonstrated experimentally on animals. Aside from Pasteur and Koch, the greater part of this work was done by Ogston, Rosenbach, Passet, Garre and Fehleisen, and so convincing was their demonstration, that the information concerning the pyogenic cocci given in Baumgarten's "Handbuch der pathologischen Mycologie" in 1887 is almost as satisfactory as that available at the present time. Moreover, between the years 1884 and 1889, the work of Carle and Rattone, Nicolaier and Kitasato resulted in the isolation of the tetanus bacillus, and the conclusive experimental demonstration of its pathogenic action.

All of these discoveries were based on animal experimentation, and indeed it may be said that none of the important advances in bacteriology would have been possible without its aid. Occasionally, enthusiastic investigators, such as Bumm, Garre, Bockhart and Fehleisen, made experiments on their own persons, and thereby still further convinced themselves of the pathogenic properties of certain pyogenic bacteria.

Following the recognition of the bacteria concerned in the production of wound infection, it became possible to test the efficiency of the various antiseptics recommended for their destruction. It is particularly to Koch that we are indebted for the fundamental contribution to the doctrine of disinfection, and for the demonstration of the great value of bichlorid of mercury. Further investigation, however, gradually materially impaired our faith in the efficacy of antiseptics, and led to the development of aseptic surgery. This resulted, on the one hand, from the demonstration of the deleterious action of disinfectants on the tissues, and on the other, from the recognition of the practical impossibility of rendering the hands absolutely sterile by means of antiseptic solutions. The realization of the latter fact led to the introduction of rubber gloves, which has enabled us to do away with all danger of infection by the hand of the operator, and together with the sterilization of dressings, instruments and suture material by means of steam, has reduced to the lowest possible limits the possibility of the introduction of bacteria into wounds.

All of these advances were based directly on the practical application of bacteriology, and this in turn owed its development solely to animal experimentation. Manning, after a careful historical review of the development of antiseptic and aseptic surgical technic, makes the same statement, and holds that in no other field have its benefits been so clearly marked as in obstetrics.

As far as I have been able to learn, Semmelweis in 1846 was the first to resort to animal experimentation in the hope of solving the problem of puerperal infection. He introduced into the freshly delivered uterus of animals, uterine discharges and peritoneal exudate from infected women, as well as the exudate from men dead of peritonitis, and in the majority of instances was able to bring about the death of the animal from infection. Animal experiments were also made by Tarnier, Mayrhofer, Coze and Feltz, Quinquaud, Orth, Heiberg, Eberth, D'Espine, Kehrer, Karewsky, Miller, Pasteur and Doléris and many other later investigators.

Of these Mayrhofer, Coze and Feltz, Pasteur and Doléris deserve especial mention. The former in 1864 observed bacteria in the interior of the infected uterus,

which he described as vibrions, and by the injection into animals of lochia containing them was able to reproduce the disease. Coze and Feltz in 1869 apparently demonstrated the presence of streptococci in the blood of women dying from puerperal fever, and cultivated them in rudimentary fluid culture media. They also produced death in animals by their inoculation. As has already been mentioned, Pasteur was the first to describe clearly, and to cultivate the streptococcus from cases of puerperal infection, and together with his collaborator Doléris effectively demonstrated its etiologic significance.

Following Pasteur, it has gradually been demonstrated that, while the streptococcus is the organism most usually concerned in the production of fatal puerperal infections, all of the pyogenic bacteria, which play a part in ordinary wound infection, may likewise give rise to them. Scarcely any one who has busied himself with their study has failed to resort to animal experimentation, and none of the recent advances along this line would have been possible without its aid.

Listerian methods were not adopted in gynecology and obstetrics until after 1875, and for the succeeding few years the chief reliance was placed on the free use of phenol for disinfecting the hands and dressings and for use as a spray. Such precautions were soon carried to ridiculous extremes, and at the acme of the antiseptic period it was thought necessary to remove all furniture from the room in which a woman was to be confined, to scrub the walls and floors with a phenol solution and to have a nebulizer spray it on the external genitalia during the second stage of labor. At the same time, disinfection of the hands was slighted, as it was believed that their immersion in a phenol solution for a few moments was sufficient to render them absolutely sterile. As these precautions did not lead to the complete disappearance of puerperal infection, the attempt was made to destroy all bacteria in the birth canal by means of vaginal and intra-uterine douches of phenol solution, or of bichlorid of mercury, after its introduction in 1881. That such practices were not without danger was soon shown by the appearance in the literature of large series of cases in which death occurred from phenol or bichlorid poisoning.

With the gradual development of clearer ideas concerning the process of infection and the limitations of disinfection in general, the employment of antiseptic methods was gradually abandoned and its place taken by the aseptic technic which we now employ, in which less and less importance is attached to chemical disinfection and increasingly more weight laid on absolute subjective and objective cleanliness.

RESULTS FOLLOWING THE EMPLOYMENT OF ANTISEPTIC AND ASEPTIC TECHNIC

Following the introduction of antiseptic methods into obstetrics, there occurred a marked diminution in the death-rate from puerperal infection, which however, was nothing like so great as in the later or aseptic period. Thus, Dohrn analyzed the results obtained in 104,278 women delivered in forty-seven German lying-in institutions between the years 1874 and 1883 inclusive, and found an average mortality of 1.37 per cent. At the beginning of the period it was 1.73 per cent., and became reduced to 0.96 per cent. at its end. Moreover, it is interesting to note that the worst results were obtained in the institutions used for the instruction of students, while the best were in those not employed for teaching purposes, the mortality averaging 1.9 and 0.56 per cent., respectively.

When compared with the mortality of 3 or 4 per cent., which characterized the previous decade, the results were most encouraging; and Dohrn felt that they probably could not be improved on, as he stated that "the mortality in lying-in hospitals will never be lowered for any great length of time to the percentage prevailing in private practice; and, if we estimate the latter at 0.6 to 0.7 per cent., the institutional mortality would still be nearly double as high. The lying-in institutions have to contend with such unfavorable conditions that such results as in private practice would never be permanently possible."

Bar stated that, following the introduction of antiseptic methods in the Maternité of Paris, the mortality fell to 1 per cent. in 1873 and to 0.8 per cent. in 1882; while Tarnier has given a very graphic picture of the conditions in the same hospital. For this purpose he distinguished three periods; namely, from 1858 to 1869, from 1870 to 1880, and from 1881 to 1889, and desig-

nating the first as the period of inaction, the second as that of fight against contagion and the third as the antiseptic period, recorded a mortality of 9.31, 2.32 and 1.05 per cent., respectively. On the other hand, at the Clinique where Depaul and Pajot, who did not believe in the bacterial nature of the disease, continued to use the old methods, as many patients died as previously.

With the gradual development of aseptic technic and more rigid precautions for the prevention of infection, better and better results were obtained, so that Mermann in 1907 was able to report a septic mortality of only 0.08 per cent. in 8,700 patients delivered under his supervision in Mannheim. Pinard in 1909 reported a net mortality of 0.15 per cent. in 45,633 deliveries in the Baudelocque Clinic during the eighteen years ending with 1908; while in the same year Markoe recorded a percentage of 0.34 in 60,000 women delivered by the Society of the New York Lying-in Hospital.

At the present time it is safe to say that in well-regulated hospitals the mortality from puerperal infection is less than 0.25 per cent. This is in great contrast with the average mortality of 3 to 4 per cent. observed throughout the world prior to the introduction of antiseptic methods, and means that only one woman now dies as compared with fifteen or twenty formerly. Moreover, the criterion of excellence in lying-in hospitals is now not so much the actual mortality as the morbidity of patients; namely, the percentage in whom the temperature rises to 38 C. or 100.4 F. during the first ten days of the puerperium.

This improvement is astounding, and at the present time it is safe to say that fewer deaths from infection occur in well-regulated lying-in institutions than in private practice, notwithstanding the fact that in the former the patients are freely used for clinical instruction. In this regard Dohrn and Florence Nightingale were poor prophets, as the former stated that such results would never be attained; while the latter held that hospitals could not be rid of puerperal infection as long as they were used for the instruction of students.

This revolution must be attributed to animal experimentation, which made possible the demonstration that definite bacteria are the cause of wound infection, and that one of its varieties—puerperal infection—is due to

the introduction of pyogenic bacteria into the birth canal of parturient women, and can be prevented by appropriate means. Of course, it may be urged that far-seeing men, such as Gordon, Holmes, Semmelweis and Tarnier realized the contagious nature of puerperal fever long before bacteriology became a science. They were not, however, able to impress their belief on the profession, and consequently no improvement was observed until the bacterial nature of the disease was clearly demonstrated. Formerly, the obstetrician groped in the dark in his attempt to identify the unknown contagion, if he even believed in its existence; while now we know exactly with what microorganisms we have to deal, and the means to adopt in order to overcome them.

At the present time, puerperal infection is no longer regarded as a visitation of Providence, but is attributed directly to the introduction of bacteria following a "break" in aseptic technic; and, whenever a case occurs in a well-regulated hospital, the director immediately begins to inquire how it happened, and, having found the source, is at once able to put a stop to further spread of the disease.

2. THE APPLICATION OF ASEPTIC TECHNIC TO OBSTETRIC OPERATIONS

The same factors which led to the disappearance of puerperal fever from lying-in hospitals and made possible the wonderful advances in general surgery, played an identical part in revolutionizing the results following the various operative procedures in obstetrics.

This is most strikingly illustrated by contrasting the results following Cesarean section and symphyseotomy or pubiotomy during the preantiseptic period and at the present time. Even as late as 1886, Dr. Robert Barnes wrote:

The Cesarean section occupies a doubtful place between conservative and sacrificial midwifery. It is conservative in its design, in its ambition; it is too often sacrificial in fact. It is resorted to with a feeling akin to despair for the fate of the mother, which is scarcely tempered by the hope of rescuing the child. It is looked upon by the great majority of obstetricians as a last desperate resource, as the most forcible example of that kind of surgery which John Hunter regarded as the reproach of surgeons, being a confession that their art was baffled.

From 1787 until 1879, when Tarnier reported his first operation under antiseptic precautions, not a single successful Cesarean section had been performed in Paris; while Lusk, in the early eighties, was the first successful operator in New York. Dr. Robert T. Harris stated that in the forty Cesarean sections performed in the United States up to the year 1860, the mortality was 52 per cent.; while Radford estimated it at 84 per cent. in the 100 operations performed in England up to that time. Indeed, as late as 1887, Harris stated that Cesarean section could be performed more safely by the horn of an infuriated bull than by the most accomplished surgeon in the best-equipped hospital in America. In support of this statement, he collected from the literature nine instances in which the abdomen of pregnant women had been ripped open by the horn of an infuriated bull, with five recoveries; whereas, only two mothers had survived the eleven Cesarean sections which had been performed in New York up to that time.

This horrible mortality was revolutionized by two factors: namely, the development of antiseptic surgery, and the description by Sänger in 1882 of a proper technic for suturing the uterine incision. The results following their adoption were so striking that Caruso was able to report that in 135 operations performed between the years 1882 and 1888, the mortality had been reduced to 25.56 per cent. Following the employment of more rigid technic and the proper selection of cases, this was gradually lowered, so that at the present time Cesarean section is undertaken by competent operators without hesitation, and gives most satisfactory results, as is indicated by the following figures: Thus, Bürger, in 1908, reported a gross mortality of 3.4 per cent. in 116 consecutive operations performed in Schauta's clinic, and Markoe one of 6.45 per cent. in 124 uncomplicated cases in the New York Lying-in Hospital. Moreover, Leopold has just recorded a gross and a net mortality of 6.2 and 3.3 per cent., respectively, in 303 operations performed in the Dresden clinic, and states that the last seventy operations were uniformly successful. In this country, Reynolds has thirty consecutive successful operations to his credit, and has pointed out that the danger is very slight if the operation is performed early, but increases rapidly with

each hour of labor, as is shown by the following analysis:

	Per cent.
82 operations before onset of labor, mortality.....	1.2
158 operations early in labor, mortality	3
49 operations late in labor, mortality.....	12

In view of such results, one may say that the mortality of Cesarean section, performed either in the last weeks of pregnancy or at the very beginning of labor, should not exceed that of ordinary gynecologic laparotomies, which is between 1 and 2 per cent. This striking revolution is due entirely to the development of aseptic surgical technic and to the restriction of the operation to uninfected women, who have not been subjected to the exhaustion incident to prolonged labor.

Exactly the same story can be told concerning symphyseotomy and pubiotomy. The former was first performed in 1777 by Sigault, and immediately afterward enjoyed a short-lived popularity, but soon gave such discouraging results that it was abandoned. Harris was able to collect reports of 70 cases up to 1858, with a maternal and a fetal mortality of 37 and 67 per cent., respectively.

The operation was resuscitated in Naples shortly afterward, and between 1866 and 1880, fifty operations were done, with a maternal mortality of 20 per cent. Following the introduction of antiseptic technic, it came into more general use, and Neugebauer in 1893 calculated that the mortality had fallen to 11.1 per cent.; while Mayer in 1908 stated that it had become still further reduced, but was still as high as 6 per cent. In view of the relatively high death-rate, and the more satisfactory results following Cesarean section, the operation gradually fell into desuetude, but was resuscitated again in 1897 under the form of pubiotomy.

Owing to the further development of aseptic technic, and the exact recognition of the character of cases susceptible to it, the mortality of pubiotomy has been kept within low limits, so that in May, 1910, I was able to collect from the literature reports of 518 operations performed by less than twenty operators, with a gross mortality of 1.9 per cent. In my clinic thirty odd pubiotomies have been done with no maternal deaths, while Roth has just reported eighty-five operations from Leopold's clinic with two deaths.

Similar improvement has occurred in the results following all other obstetric operations—forceps, version, induction of labor, *accouchement forcé*, etc. Unfortunately, it must be admitted that owing to the comparative immunity from danger there has developed a tendency on the part of many to resort unnecessarily to operative procedures, when Nature alone would have brought about a happy termination. Notwithstanding such tendencies, however, the general result is most creditable, and stands out in wonderful contrast to that of the past, and has each year been the means of saving the lives and diminishing the sufferings of thousands of women.

In this connection, one cannot reiterate too strongly that all of these advances must be traced back to the same cause, namely, the development of bacteriology and of aseptic surgical technic, both of which in turn are entirely dependent on the employment of animal experimentation.

3. THE RECOGNITION OF THE BACTERIAL NATURE OF CERTAIN INFECTIOUS DISEASES IN THE NEW-BORN CHILD

In times past, probably the most important disease of this group, occurring in lying-in hospitals, was the so-called puerperal fever of the new-born child. This condition, which was studied particularly by Schindler, Troussseau, Lorain, Hecker and Bühl, Müller and others, occurred particularly when the hospitals were ravaged by puerperal fever, and was due to the infection of the child during labor, or shortly afterward. In the first case, the amniotic fluid became infected during the course of a prolonged labor with concomitant infection of the air passages of the child with subsequent development of bronchopneumonia; while in the latter case, infection occurred through the stump of the umbilical cord. In either event, the disease was extremely fatal and only a small proportion of the infected children escaped, while autopsy showed one or more of the protean manifestations of wound infection; especially, bronchopneumonia, pleurisy, peritonitis, meningitis, erysipelas, pyemia or general septicemia.

Some idea of its incidence may be gained from the fact that a mortality of 7.62 per cent. was observed in the 18,329 children delivered in the Vienna Hospital

prior to the work of Semmelweis. Following the employment of the precautions against puerperal fever which he recommended, the fetal death-rate was so markedly reduced that Bednar, who had charge of the Foundling Asylum, stated "that the disease of the children [blood sepsis] had almost entirely disappeared in consequence." Lorain noted a similar connection in the Maternité of Paris and reported that in 2,567 labors occurring during the year 1854, 5.7 per cent of the mothers and 7.5 per cent. of the children were lost, and the high mortality continued until antiseptic precautions were introduced by Tarnier. Hugenberger, likewise, estimated that the average fetal mortality in the St. Petersburg Hospital was 2.6 per cent., which rose as high as 14 per cent. during puerperal fever epidemics; while Hecker and Bühl observed an even higher death rate.

At the present time this condition is observed but rarely, and then only in the case of women who are admitted to the hospital already infected, when the bacteria contained in the amniotic fluid gain access to the child and give rise to infection.

As long as epidemics of so-called fetal puerperal fever occurred, comparatively little attention was paid to the actual mode of infection, but with the subsidence of the disease, the question was more carefully studied. It was then found that the portal of entry was usually through the stump of the umbilical cord, and this type of infection persisted for several years after puerperal fever had practically disappeared from lying-in hospitals.

Occasionally it caused a terrible mortality, and Paquy refers to the experience of Meynet, who lost 17 per cent. of the children cared for in a crèche in Lyons. Moreover, Runge stated that he had observed a mortality of 4 per cent. in Strassburg, as well as nineteen deaths in the Charité in Berlin during the first six months of 1880. His investigations showed that the umbilical arteries were usually involved, while infection occurred only exceptionally through the vein.

Following the introduction of antiseptic methods of caring for the stump of the umbilical cord, this variety of infection rapidly disappeared, so that at present in well-regulated hospitals it occurs only once in many hundred cases. At the same time, owing to the faulty

technic, so often observed in this regard, it still occurs too frequently, and should always be suspected whenever a child dies without well-marked symptoms indicative of some definite disease, when autopsy will usually show the umbilical arteries distended by suppurating thrombi, which have given rise to peritonitis or a general systemic infection. We now hold that the condition always results from bacterial invasion, which is usually streptococcic in character; and we are forced to attribute the great diminution in its occurrence to the recognition of its true nature, which was made possible only by the development of bacteriology, which is based on animal experimentation.

Formerly, large numbers of new-born children died each year from tetanus, and Collins stated that during his mastership at the Rotunda in Dublin, one-fifth of all children, dying within the first fortnight after delivery, perished from it. He also referred to the epidemics observed during the mastership of Dr. Clarke, who said "At the conclusion of the year 1782, of 17,650 infants born alive in the hospital, 2,944 died within the first fortnight, and nineteen out of twenty of these died of nine-day fits." This indicates a total fetal mortality of 16.6 per cent., of which 95 per cent. was due to tetanus. This epidemic was held in check by the greatest attention to ventilation and cleanliness, but that the disease was not entirely eradicated is shown by the experience of Collins forty or fifty years later.

Similar epidemics have also been noted in other parts of the world, one of the most remarkable having occurred in the Island of St. Kilda, and was described by Mitchell in 1865. In this epidemic, 67.2 per cent. of all new-born children died, and the horrible death-rate continued until antiseptic methods of caring for the cord were introduced, when Turner reported that dusting the stump with iodoform had led to its complete disappearance. Until comparatively recently, the negro race in the South was often decimated by tetanus neonatorum, and the extent of its ravages may be gained from the following quotation from Grier:

We have known more than one instance in which, of the births for one year, one-half became the victims of this disease, and that, too, in spite of the utmost watchfulness and care on the part of both planter and physician. Other places are more fortunate, but all suffer more or less, and the planter who

escapes a year without having to record a case of trismus nascentium may congratulate himself as being more favored than his neighbors, and prepare himself for his own allotment, which is surely and speedily to arrive.

Similar conditions likewise obtained in Jamaica, and as early as 1835 Maxwell reported:

From observations I have made for a series of years, I found that the depopulating influence of trismus neonatorum was not less than 25 per cent. It scarcely has a parallel on the bills of mortality.

Unfortunately, the same condition still prevails, as Pescay recorded identical results in 1900. How seriously the disease was formerly regarded is shown by the fact that the 1889 edition of Dr. J. Lewis Smith's textbook on diseases of children contained a chapter of twenty-one pages on the subject.

Prior to the isolation of the tetanus bacillus, the condition was attributed to filth and impure air, but with the recognition of its specific cause and the employment of aseptic methods in the treatment of the umbilical cord, it has practically disappeared, and I have never encountered a case in more than 10,000 newly-born children under my supervision. This advance, just as all the others, to which I have referred, must be attributed solely to the employment of animal experimentation, for without its aid the tetanus bacillus could not have been isolated, nor its characteristic pathogenic properties demonstrated.

4. THE BIOLOGIC TESTING OF ERGOT

This drug, which is now so freely employed throughout the civilized world for the control of postpartum hemorrhage by the stimulation of uterine contractions, was first described medically by Dr. John Stearns of Waterford, N. Y., in 1808; while we owe the first dissertation on its physiologic action to Prescott of Boston in 1822. Following this, its complicated constitution has given rise to almost countless investigations, and pharmacologists are not yet in agreement concerning its active principles. Some idea of the amount of work done on the subject may be gained from the fact that Grünfeld, in his study, which appeared in 1892, required fourteen pages arranged in double column to contain a list of the publications of the previous twenty-five years.

Some of the most important contributions to the action of the drug we owe to Kober, Jacoby, Grünfeld, Barger and Dale. Ever since its employment for medicinal purposes very conflicting statements have been made concerning its active principles and physiologic action, and it was not until after the careful studies of Grünfeld that the cause for the discrepancy was recognized. He found that the powdered drug rapidly lost its medicinal properties; and while a certain preparation might be very potent when first prepared, it so rapidly deteriorated as to be practically without physiologic effect after being kept for four or five months. The recognition of this fact led to the necessity of devising some method for testing the physiologic activity of the various preparations of ergot before putting them on the market.

Unfortunately, no method of chemical analysis or assay has as yet been devised to enable manufacturing chemists or physiologists to determine the value of a given preparation, so resort was necessarily had to biologic or physiologic tests for the purpose. From the earliest times it had been noted that an efficient preparation would lead to marked bluing, and eventually to gangrene of the comb and wattles of the rooster; although later investigations tended to show that such a result was not necessarily an index of its action on the uterus, as it had been demonstrated that the gangrene-producing properties were quite independent of those causing uterine contraction. Consequently, other modes of investigation became necessary. Kурдинowski determined its physiologic activity by testing its effect on the isolated uterus, Kehrer, instead, used thin slices from the uterus of freshly killed pregnant animals, while Cronin and Henderson studied in animals its effect on the blood-pressure.

According to Crawford, most manufacturing chemists at the present time test its efficiency on the cock's comb and wattles; although he states that it would be preferable to employ the living uterus, as recommended by Kурдинowski and Kehrer. In any event the manufacturing chemist must resort to some such form of animal experimentation in testing every specimen of ergot which he uses for the manufacture of the preparations sold to the public; and that means that no woman can take ergot for the control of hemorrhage without being the

recipient of at least one of the advantages which has been gained from animal experimentation.

5. THE DEMONSTRATION OF THE INTERNAL SECRETION OF THE OVARIES

Although the atrophic changes occurring in the internal genitalia following the menopause, or the operative removal of the ovaries, were long ago recognized, the possibility that they were a manifestation of the disappearance of an internal secretion, formerly elaborated in those organs, was not suspected until after the appearance of Brown-Séquard's suggestive article on the subject.

As long as such a supposition was not supported by facts capable of demonstration, it was not possible to be sure of its correctness, or to deny that the changes in question were neurotic in origin. The experimental work of Knauer, Gregoriff, Mandl and Bürger, Marshall and others, however, conclusively demonstrated that the ovaries elaborate a definite secretion, which serves to regulate the nutrition of the internal genitalia, as well as to exert a definite effect on the entire organism. Moreover, it was clearly shown that the organs could be removed from their usual site and transplanted to other distant portions of the body, and still prevent the degenerative changes which usually follow their removal. As all nervous connections had been severed at the time of operation, it was evident that the only manner in which such an influence could be exerted was by means of an internal secretion, which gained access to the blood-current.

Other experiments showed that the transplanted ovaries functioned perfectly, and if implanted in a suitable location, produced ova which could be fertilized. Such findings were not merely of scientific interest, but possessed a distinctly practical bearing in that they suggested the possibility of transplanting the ovaries in human beings, as well as the employment of ovarian tissue extract in the treatment of various conditions resulting from imperfect ovarian secretion, more particularly the distressing symptoms which frequently accompany the menopause or follow the removal of the ovaries. Not a few operators, when obliged to remove both tubes and ovaries on account of disease, have implanted healthy portions of the latter on the uterus or broad

ligaments, in order to prevent the occurrence of an artificial menopause in young women. Less frequently, the ovaries of one woman have been implanted into another, in the hope of reestablishing the menstrual function, or even making possible the occurrence of pregnancy. The former result has been attained in numerous instances, while the latter has resulted successfully in at least two cases. Those who are interested in the subject are referred for details to Martin's article which contains full references to the literature up to 1908.

Fraenkel, in 1903 and 1910, published two important contributions on the function of the ovaries, which were based entirely on animal experimentation. He apparently showed that the corpus luteum should be regarded as a temporary gland which produces an internal secretion, whose function, at least in part, is to bring about the changes in the internal genitalia necessary to permit the implantation of the fertilized ovum. Furthermore, his experiments rendered it probable that the continuance of the secretion was essential for the preservation of pregnancy during its early periods, but was not necessary later; and thus afforded an explanation for the clinical observation that removal of the ovaries early in pregnancy is usually followed by abortion, whereas their removal later has no effect.

His work also suggested a possible explanation for the not infrequent lack of success in the therapeutic application of ovarian extract, since, if its action were solely due to the presence of corpus luteum tissue, efficiency could not be expected if the preparation consisted only of ordinary ovarian stroma. For this reason, he recommended that in future the so-called ovarian tissue tablets be made exclusively from corpora lutea, and not, as formerly, from the entire substance of the ovary; and clinical reports seem to indicate that his premises were correct.

6. *EXPERIMENTAL STUDIES CONCERNING THE NATURE OF THE TOXEMIAS OF PREGNANCY*

Up to twenty years ago our ideas concerning the nature and etiology of eclampsia were but little clearer than in 1843, when Lever first described the presence of albumin in the urine of eclamptic women, and held on that account that it was merely a variety of nephritis.

Following the experiments of Rivière in 1888, and those of Tarnier and Chamberlent a few years later, in which it was apparently shown that the toxicity of the urine of eclamptic women was greatly decreased for experimental animals, while that of the blood-serum was markedly augmented, the belief gained ground that the condition was toxemic in character, and was due to the retention within the organism of certain substances which were ordinarily excreted through the kidneys. Following these observations, the experimental study of eclampsia has occupied the attention of large numbers of investigators, and although the subject has not yet been thoroughly elucidated, the conviction is growing stronger and stronger each year that the disease is a toxemia, which is in some way dependent on the pregnancy, and in all probability connected with abnormal processes either within the body of the fetus or placenta.

It would carry us too far afield to attempt even to enumerate those who have taken part in such investigations, but the contributions of Volhard, Veit, Hofbauer, Lichtenstein, Freund, and Thies deserve especial mention. Moreover, we might refer, in this connection, to the fact that it is only by means of animal experimentation that we have learned the part which the secretion of the thyroid gland plays in regulating the metabolism of pregnancy.

Although none of these experimental investigations have entirely cleared up the etiology of the affection, they have nevertheless served to impress on us its toxemic nature, and have taught us that the treatment *par excellence* consists in the prompt evacuation of the uterus. Moreover, I consider that if the matter is ever to be settled, it can only be accomplished by the aid of animal and biochemical experimentation.

7. THE EXPERIMENTAL PRODUCTION OF FETAL DEFORMITIES

If it is permissible to designate as animal experimentation the various procedures to which the fertilized eggs and the developing embryos of various animals are subjected for the purpose of producing anomalies of development, we can point to a field which has not only markedly advanced our knowledge concerning the normal mechanism of growth and the mode of production of monstrosities, but one which is destined to add greatly to the comfort of the human race.

In times past, the birth of monsters or of children afflicted with congenital deformities was attributed to the anger of the gods, to witchcraft or to some malign influence to which the pregnant woman had been subjected. With the advance of knowledge and the passing of superstition, such views gradually disappeared; but, on the other hand there is scarcely a woman in America at the present time, who does not firmly believe in the doctrine of maternal impressions, and who, in case of the birth of a monstrous or deformed child, will not attempt to trace its origin to some unpleasant sight or experience to which she had been exposed during pregnancy.

Such a belief is not limited to women, but is likewise shared by most medical men in this country, as is shown by the fact that as late as 1889 Keating's "Encyclopedia of Diseases of Children" contained a long article in its favor. Moreover, not a few works on obstetrics direct that the pregnant woman should be guarded from unpleasant sights of all kinds.

Persistence in the belief in maternal impressions is each year a source of great unhappiness to thousands of women, who, after some trivial occurrence, such as seeing a mouse or a rabbit, are convinced that their child will be "mouse-marked" or hare-lipped in consequence, and who do not dismiss their fears until a perfectly normal and well-formed child has been born. Indeed, I feel that I am safe in stating that no one who has not considerable experience with pregnant women can appreciate the extent of the suffering and dread resulting from this superstition.

The new science of experimental embryology and teratology has shown clearly that such an occurrence is impossible, as in the vast majority of cases, the changes which were attributed to it developed in the earliest periods of pregnancy, whereas the "maternal impression" to which a given deformity was attributed did not occur until a much later date.

Geoffroy Saint-Hilaire, Allen Thompson and Fére were the first investigators to attempt the production of deformities by subjecting the developing egg to various conditions, but it is only within the last twenty-five years that the matter has seriously engaged the attention of scientific men. During this period, however, the work of Pflüger, Dareste, Roux and Born has put the subject

on a scientific basis, as they have shown beyond question that pricking certain portions of the segmenting ovum with a needle, encircling it with a ligature, or subjecting it to certain chemical influences, will inevitably be followed by definite deformities, and they were enabled in this way to produce at will, not only single, but double monsters of the most varied type.

Further research along these lines has been particularly prolific in this country, and the investigations of Loeb, Morgan, Wilson, Bardeen, Harrison, Stockard and many other, has led to most astounding results, which have revolutionized our ideas of teratology. These investigators have shown beyond peradventure that practically all of the deformities with which we meet at the time of labor can be produced at will by subjecting the early ovum or embryo to various procedures. Thus, it is possible to produce spina bifida, cyclops, headless or double monsters, as well as those lacking extremities or having accessory ones, merely by changing the experimental conditions.

As the result of these investigations, it has been definitely proved that, with the exception of certain well-marked hereditary deformities, the great majority of monsters are the result of some interference with the normal growth of the ovum in the days immediately following conception, and not to later influences. Moreover, Mall in a study of four hundred early human abortions found that 38 per cent of them were pathologic, and that many presented deformities which were inconsistent with further life. He estimates that in about 7 per cent. of all pregnancies the ovum is abnormal, and as the changes began in the early weeks it is manifest that "impressions" occurring at a later period of pregnancy could have no part in their production.

Indeed, at the present time the evidence available seems to indicate that the entire doctrine of maternal impressions is a superstition which will sooner or later entirely disappear, and this result will be hastened as the work of the experimental teratologist becomes generally known.

CONCLUSION

In conclusion, it may be said that while the benefits which obstetrics have derived from animal experimentation are not immediately apparent, they are nevertheless very real, and have led to revolutions in obstetric

practice and to results which are but little realized by the general public. I think that I am safe in asserting that had animal experimentation led to nothing more than the discovery of the bacterial nature of puerperal fever, whereby a means was provided for doing away with its former hideous mortality, it would abundantly justify the sacrifice of all the animals which have thus far been used for experimental purposes. Think of the millions of lives which have been saved, if we accept Boehr's calculation, that formerly every thirtieth married woman has inevitably doomed to perish from puerperal infection. Fortunately, this is not the only benefit even in obstetrics, which can be ascribed to animal experimentation, as the increased security following operations and the marked decrease in the mortality of new-born children are equally attributable to it. Indeed, it may be truthfully said that every time a physician cleanses his hands preparatory to attending a woman in labor, he is rendering a tribute to animal experimentation; although unfortunately, the world at large, which benefits from it, does not recognize its significance. I feel that there is every reason to expect that animal experimentation will play as large a part in developing our ideas in the future as in the past, and I confidently believe that the problem of eclampsia and the other toxemias of pregnancy, as well as the cause of labor and all that that implies, will eventually be solved by its means.

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Some Characteristics of Antivivi- section Literature

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Some Characteristics of Antivivi- section Literature

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SOME CHARACTERISTICS OF ANTIVIVISECTION LITERATURE

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Last year I obtained from the four prominent anti-vivisection societies of the country¹ copies of the pamphlets and leaflets which they distribute widely to school teachers and clergymen and other influential but medically uninstructed persons. For about two years I have also collected letters and articles which have been published on the subject in the daily press and in magazines. This literature can be considered with reference either to the justice of its claims, or to the fairness of its methods. For the present I wish to hold a consideration of the merits of the controversy in a secondary position and to examine these accumulated writings as to some of the tactics which they display.

To go through this matter with patience is a difficult task. Dreary iteration of the same opinions, the same "eminent authorities," the same tales, characterizes the society publications; and these publications, sent broadcast, are used again and again for texts, examples and references by contributors to newspapers and journals. Surely this is vain repetition, for any one whose intelligence is not stupefied with weariness can perceive that if the identical names and phrases, and the identical instances have to be continuously cited the cause must be short of both men and ammunition.

One of the most impressive exhibits which the anti-vivisectionists make is the list of physicians whose opinions they quote. This list is worth examining with some care. In doing so we should keep in mind that the great victories of experimental medicine have come

1. The New England (Boston), the New York (New York City), the American (Philadelphia), and the Vivisection Reform Society (Chicago).

since 1850, and in largest number since 1880; and furthermore, that this illustrious period of medical history is practically coincident with the use of anesthesia, not only in surgery, but in experimentation as well.

Many of the physicians whose opinions are quoted are dead. Some died long ago, others who have passed away more recently received their formal education in medicine before the period I have just mentioned. Of all the names cited the most renowned is that of Sir Charles Bell, born in 1774 and dead nearly 70 years, known for his discovery of the distinct functions of the dorsal and ventral roots of spinal nerves, and for his study of the functions of the fifth and seventh cranial nerves. In each of these important investigations his final proof was secured through experiments on animals. His own description of his greatest discovery is as follows: "On laying bare the roots of spinal nerves I found that I could cut across the posterior fasciculus of a nerve which took its origin from the posterior portion of the spinal marrow without convulsing the muscles of the back, but that, on touching the anterior fasciculus with the point of a knife, the muscles of the back were immediately convulsed."² On this experiment, done a hundred years ago, nearly forty years before the use of general anesthesia, his fame rests. To quote him to-day as opposed to the use of the experimental method is, under the circumstances, not only a contradiction of his own practice, but a gross anachronism.

Another name which, like the words of Humpty Dumpty, ought to be paid extra because so much over-worked, is that of Henry J. Bigelow. He was born 92 years ago and has been dead for 20 years. The address so often quoted was delivered in 1871—back four decades. According to the testimony of his colleagues in the Harvard Medical School, his views on vivisection were apparently based on what he had seen at the veterinary school at Alfort, France, in the pre-anesthesia days, and he had not controlled these early impressions by any experience in a modern laboratory. A close associate has testified that during the last years of Dr. Bigelow's life he never heard him say a word against animal experimentation.³ Furthermore, in a letter which

2. *A New Idea of the Anatomy of the Brain*, London, 1811.

3. *Animal Experimentation*, Boston, 1902, pp. 48, 74.

has been little noticed Dr. Bigelow objected sharply to the lack of discrimination among antivivisectionists. "The confounding of a painful vivisection," he wrote, "and an experiment which does not cause pain—either because the animal is under ether, or because the experiment itself is painless, like those pertaining to the action of most drugs, or because it is a trivial one and gives little suffering—has done great damage to the cause of humanity."⁴ And yet Dr. Bigelow is continually cited as a famous surgeon who was opposed to experiments on animals.

One other medical name appearing again and again in antivivisection writings is Lawson Tait (born 1845, died 1899). He has been described by a competent and trustworthy surgeon as a "man of wild statements."⁵ Certainly that characterization is justified by Tait's promise that if he could get enough disease germs he would gladly use them as dressings for surgical wounds, and also by his absurd denunciation of Koch, Pasteur and Lister—the leaders of modern medicine—as men who had "not only hindered true progress, but covered the profession with ridicule." This extraordinary attitude, together with his opposition to the use of animals for medical research, is perhaps explained by a line in the sketch of his life—"He enjoyed being in a minority, and this led him to champion many lost causes."⁶

Other physicians whose opinions are quoted are of less note. There is Dr. Charles Clay, born in 1801, "interested in geology and archeology and collector of fossils." There is Dr. Charles Spooner, born in 1806, veterinary surgeon. There is Dr. John Elliotson, born in 1791, who alarmed his colleagues by administering extravagantly large doses of supposedly poisonous medicines; also mesmerist, and founder of a mesmeric hospital. There is Dr. J. E. Garretson, born 82 years ago, and Dr. Elizabeth Blackwell, born 89 years ago. There is Sir William Fergusson, M.D., born more than a century since, said to be ill-advised in some expressions of opinion, "especially in matters requiring more knowledge of physiology and hygiene than he possessed." There is Charles Bell-Taylor (dead in 1909, aged 80), who originated the widely quoted sentence, "Pasteur does not

4. *Anesthesia : Addresses and Other Papers*, Boston, 1900, p. 371.

5. *Animal Experimentation*, Boston, 1900, p. 47.

6. *Dictionary of National Biography*.

cure hydrophobia, he gives it;” and who, ignoring our great debt to animals for the medicines that induce sleep, for all those that give us local freedom from pain, for physostigmin, amyl nitrite, epinephrin, and many others, told his antivivisection admirers that experiments on animals have yielded us no knowledge of drugs. There is Sir Richard Owen, M.D., comparative anatomist and zoologist, born in 1804. There is Dr. John Abernethy, who died in 1831! There is J. J. Garth Wilkinson, born 98 years past, holder of an honorary M.D. degree, poet, mystic, expositor and editor of Swedenborg, author of “Improvisations of the Spirit,” “Isis and Osiris in the Book of Respiration.”⁷

In antivivisection literature the opinions of these persons are presented with no reference to the time when they were living and with no indication of the interests other than medical which filled their lives. The ingenuous reader takes his cue from the words of the pamphlet that they are “men of the greatest eminence among the vast number of physicians and surgeons who have opposed vivisection,” and wonders how doctors can so profoundly disagree.

Among the living medical men quoted by the anti-vivisectionists, Sir Frederick Treves is most prominent. In 1898, he stated incidentally that some experiments which he had performed on the intestine of the dog had done little but unfit him to deal with the human intestine. This was of course merely his personal experience, and can readily be offset by that of other experienced surgeons who testify to the exact opposite. Indeed there is probably no field of surgical manipulation that has benefited more by animal experiments than that of the gastro-intestinal tract. Sir Frederick was quick to point out the false implication placed on his remarks.

“Those who are familiar with the controversial methods of the antivivisection party,” he wrote, “will not be surprised that certain of my remarks have been cunningly isolated from the context, and have been used in advertisements, pamphlets and speeches, to condemn all vivisection experiments as useless. The fallacy of vivisection can hardly be said to be established by the failure of a solitary series of operations dealing with one small branch of practical surgery. No one is more

7. The data given above were found in the Dictionary of National Biography.

keenly aware than I am of the great benefits conferred on suffering humanity by certain researches carried out by means of vivisection.”⁸

That was written more than eight years ago, yet Treves still continues to be quoted as another of the eminent surgeons who have opposed vivisection.

What I have been able to learn about the other living “physicians and surgeons of greatest eminence,” quoted as hostile to experiments on animals, has come mainly from the publication, “Who’s Who.” Since the notices in this volume are little autobiographies, I should not be accused of employing the last resort of a losing advocate—the abuse of the opposing counsel—if I quote what these persons say about themselves. Dr. Arabella Keneally sets herself down as novelist and contributor to magazines, author of “Molly and Her Man of War,” “Some Men are Such Gentlemen,” and other volumes. Dr. W. Gordon-Stables describes himself as novelist, journalist, professional writer for 24 years, author of 136 books with serial novels; “In the Dashing Days of Old” and “The Pirates’ Gold” are cited as examples. Dr. W. R. Hadwen is secretary of the British Union for the Abolition of Vivisection, public advocate of the repeal of the Vaccination Acts and the prohibition of experiments on animals; is engaged in reform movements relating to temperance, food, hygiene, sanitation, education, and burial laws; he finds his recreation in changing his occupation. Dr. Edward Berdoe, born 74 years ago, reports himself as a writer; author of Browning studies, “Browning and the Christian Faith,” “A Browning Primer,” “The Browning Encyclopedia,” “The Biographical and Historical Notes to Browning’s Complete Works,” and several other books; also editor of the “Zoophilist.” Dr. Josiah Oldfield, a lawyer, and senior physician to the Lady Margaret Fruitarian Hospital, strong advocate of the fruitarian diet; author of “Flesh Eating as a Cause of Consumption,” “Butchery and Its Horrors,” and other volumes. Dr. J. D. Buck, 72 years old, president of the Theosophical Society of Ohio, author of “Nature and Aims of Theosophy,” “Mystic Masonry,” “Why I am a Theosophist.” Dr. Stephen Townsend, novelist, surgeon, and actor, on the stage for years, playing prominent rôles in “Sowing the Wind,” “Slaves of the Ring,” “Black Tulip,” and others.

This completes the list of "eminent" physicians and surgeons who have opposed vivisection, concerning whom I have been able to find any characterization whatever—the rest are not of sufficient importance to be mentioned in any of the dictionaries or cyclopedias of biography that I have searched through for information. And this is the array of medical experts who have denounced the method of investigation which, according to Osler, "did more in the half-century between 1850 and 1900, to emancipate medicine from the routine and thraldom of authority than all the work of all the physicians from the days of Hippocrates to Jenner."

I do not wish to imply that unless a physician does nothing but practice medicine his opinions on medical matters are of little value. But when a person with a medical degree denounces the antitoxin treatment of diphtheria, I am interested to learn that the time of that person is spent in composing romances. When another declares that the cruelty of experimentalism is "horrible to contemplate," I am better able to value his words when I know that instead of "contemplating," he has for 24 years been industriously writing and has now to his credit nearly seven-score volumes. A third expert who declares experiments on animals useless and unscientific, I understand better when I find that he is a professional agitator, working for the abolition of vivisection and for the destruction of community barriers against small-pox. The sounding phrases, "Pasteurian quackery," "antitoxin nostrum," "vivisection founded on cruelty, supported by falsehood, and practiced for selfish ends," have less significance when I realize that they are the expression of an aged man who has devoted his life to studying, annotating, and editing Browning's poetry. Again, in reading the grotesque exuberance of the fruitarian lawyer—that "vivisection takes no note of pain; its spirit is not healing, but killing; its object is not to relieve pain in the victim, but to cause it"—I wonder in precisely what way fruitarianism and the law have given him intimate acquaintance with the subject he so roundly denounces. And finally, when the theosophic propagandist, past his three score years and ten, unites with the actor-novelist-playwright in declaring that "scientifically" experiments on animals are useless, I have a basis for seriously sus-

pecting that they are not trained to judge these matters scientifically.

If now we examine this list, we find that it is made up of persons long-since quick, or long-since dead, persons who have not been opposed to vivisection in any unqualified sense, persons whose eminence in literature and art was the only eminence they possessed, and persons so obscure as not to be noticed in any manner whatever, except in the pages of an antivivisection leaflet. When we consider that every advance in medicine, like every advance in other realms, has suddenly revealed the reactionaries, the great marvel is that there are not medical men of real prominence who will support the antivivisection cause. But if "among the vast number of physicians and surgeons who have opposed vivisection," those we have just investigated are "of greatest eminence," surely the professional endorsement is insignificant.

Demonstration that many of their experts have no respectable qualifications for testifying will not, I believe, cause the antivivisectionists to withdraw either the names or the opinions of these men from circulation. Sir Frederick Treves called attention to their adroit misuse of his remarks more than eight years ago. Instead of respecting his expression of direct disapproval of their cause they have continued classifying him as an opponent of vivisection. The ignoring of Treves' correction is a thoroughly characteristic maneuver on the part of the agitators. Other examples are numerous. Commenting on an experiment by Dr. H. P. Bowditch, in which the peripheral end of a nerve, which had been severed under ether, was stimulated, Mr. P. C. Peabody stated, "It will be readily seen, even by the casual reader, that it involves an amount of agony beyond which science is unable to go and to approximate to which is impossible except by a person who has devoted long years to the study of nerves." Fifteen years have passed since Dr. Bowditch plainly pointed out the utter absurdity of the assumption that even the slightest pain could have been inflicted by stimulating a piece of nerve separated from the central nervous system,⁹ and yet the New England Antivivisection Society was last year still distributing this ancient slander.

⁹. Communications of the Massachusetts Medical Society, 1896.
p. 43.

Ten years ago Dr. W. W. Keen,¹⁰ in a paper of admirable simplicity and directness, laid bare instances of repeated interpolations, mistranslations, and garbled, inaccurate accounts of experiments in a single antivivisection publication. What was the effect? To what degree have ten years been sufficient for the development, in antivivisectionists, of respect for the facts?

In a pamphlet now being circulated I find mentioned Dr. Berkley's observations on the effects of administering thyroid extract to insane patients. Although Dr. Keen showed that the therapeutic use of thyroid extract varies between 15 and 60 grains per diem, and that Dr. Berkley's maximum dose was only 15 grains per diem, the pamphlet does not distinguish between the toxic effects of these small doses in some cases and the beneficial effect in others, but declares that Dr. Berkley was "poisoning" his patients. It goes on to state, "Two patients became frenzied, and of these one died before the excitement had subsided." In the original the sentence is completed by the words, "the immediate cause of the exitus being an acute disseminated tuberculosis." The absurdity of attributing death by galloping consumption to thyroid tablets, which had not been given anyhow for seven weeks, was clearly explained by Dr. Keen in his paper a decade ago: He did not emphasize the wrong done to Dr. Berkley by the crafty mutilation of a sentence. Of course, a decent sense of honor would have impelled an instant correction of this wrong, yet the antivivisectionists have continued these ten years to deceive the credulous public without any moving consideration that their imposture involved a man's good name.

Another statement in the pamphlet is as follows:— "Dr. A. H. Wentworth, senior assistant physician to 'The Infants' Hospital,' Boston, made forty-five vivisections, tapping the spinal canals of children, many of whom died." Unless the writer of this statement intended to intimate that there was a connection between the death of the children and the tapping of the spinal canal, the statement is without significance in an antivivisection publication. A careful reading of Dr. Wentworth's paper shows that the tapping of the canal, which is now (though it was not then) a common routine procedure, had no harmful effects whatever. To be

sure *some* of the children died later, but in every fatal instance the cause of death, which had no relation to the operation, was definitely determined and stated. All these facts Dr. Keen pointed out ten years ago. What was the result? The story with its evil insinuation is still circulated everywhere by the antivivisectionists, again without any observable respect for the facts, or regard for an honorable reputation. Even this exhibition of hostility has not proved a sufficient outlet for antivivisection feeling, for in the *Journal of Zoophily*, April, 1910, p. 44, Dr. Wentworth is referred to as having experimented "on between forty and fifty little children in the 'Children's Hospital' of that city (Boston) *every one of whom died* after the performance of his operation."

Three years have passed since the attention of officers of the New York Antivivisection Society was called to the fact that by suppressing mention of anesthetics in experiments they described, they were giving a wholly false impression of the way in which these experiments were conducted. Again two years ago Dr. F. S. Lee indicated in a public letter¹¹ that the society, in spite of having had a full year in which to correct these misrepresentations, was intent on its policy of deluding the public. I have recently had occasion to examine again the pamphlets which the society is distributing—the misrepresentations are still there, unchanged.¹² Details of operations by Dr. W. S. Halsted are quoted, and although the original account expressly stated that anesthetics were employed, the pamphlet does not even suggest them. Selections taken here and there from Dr. G. W. Crile's report of his experiments on surgical shock are presented, again with no intimation of anesthesia; and this in spite of Dr. Crile's printed statement that "in all cases the animals were anesthetized," and also in spite of the testimony of Dr. F. W. Goodbody¹³ and of Sir Victor Horsley¹⁴ (in whose laboratory, under the

11. *New York Evening Sun*, March 12, 1909.

12. These publications, which contain also the statements about Dr. Wentworth and Dr. Berkley above mentioned, were sent to a friend of mine in November, 1910, with a letter from the president of the New York Antivivisection Society proclaiming, with reference to the pamphlets: "You may rely on them as being absolutely accurate and authentic."

13. *London Times*, March 13, 1902.

14. *Minutes of Evidence*, English Royal Commission on Vivisection, 1906-08, Questions 15893-7, 16220-2.

English antivivisection law, much of the work was done) that the animals, though sometimes exhibiting reflexes, were completely insensible to pain.

The society furthermore continues to suggest that one can only imagine "how intense the suffering" which caused a cat at the Rockefeller Institute to "spend the day jumping on and off the furniture"—when in fact, as Dr. Carrel explained¹¹ two years ago, the animal was a young cat, in perfectly normal health, manifesting its natural playfulness.

From these specimens of persistent disregard of fair treatment, when can we expect that misstatements and Two years are evidently not enough for the antivivisectionists, even if publicly exposed, will be withdrawn? •
tionists to manifest this sense of honor, nor are ten years, nor fifteen. I have cited instances in their literature, instances of grossly garbled descriptions of the work of medical men, the inaccuracies in which have been clearly demonstrated for these long intervals, without, however, any sign of a tendency on the part of the prevaricators to reconstruct their statements in conformity with the facts. Experience has proved that the false story once well told, need not be withdrawn or altered, even if its falsity has been exposed, for that part of the public that likes to be humbugged is ready to read and listen and yield its humble credence.

The fundamental wrong committed by the antivivisectionists in their agitation against medical research is the presentation of a misleading issue. They deny that any utility has come from animal experimentation, they describe the experiments as horrible torturing of dumb brutes, and then they ask if this futile cruelty shall be permitted to go on. If this really were the whole story, few would hesitate on which side to stand. Every decent man and woman is opposed to cruelty; every decent human being winces at the thought of inflicted pain. It is for this reason that the picture of the fastened dog makes such a powerful appeal. But this is not the whole story. As I have pointed out elsewhere, it would be as fair to display a picture of Grenfell fighting his faithful dogs and stabbing them to death, labelled "Is this the way to treat your pets?" as it is to represent animal experimentation without its motives and without its triumphs. Grenfell, in his struggle on the ice-pan,

stabbed his dogs¹⁵ to save his own life, and every man with common sense commends the bravery, the resourcefulness and the proper sense of values of this missionary hero. That is what any worthy man who sees straight would try to do if he were cornered and had to spend his own life or that of lower animals. Precisely that is the issue which the investigators see. And they know also that by the sacrifice of some animals the chance of life and health for mankind and for myriads of other animals as well, has been enormously enlarged. Read the articles, written recently by experts in the several fields, telling the relation of animal experimentation to the treatment of diphtheria and tetanus, to meningitis, rabies, small-pox, to dysentery and cholera and typhoid fever, to plagues, tuberculosis, syphilis, to the disturbances of internal secretions, to our knowledge of the action of drugs, to surgical technic, to childbirth, to hygiene and preventive medicine—read these articles¹⁶ and learn what the animals have done for their fellow creatures. Just because they have rendered such immeasurable service do we turn to them for further aid. Of the animal thus used Professor William James has written with illuminating insight, “If his poor, benighted mind could only be made to catch a glimpse of the human intentions, all that is heroic in him would religiously acquiesce.”¹⁷

Before the antivivisectionists can command the respectful attention of intelligent people they must fundamentally change their tactics. They must clear their literature of the anachronistic hostility of men long since dead, men who had no conception of the merciful procedures of modern experimentation, nor of its life-giving results. They must rid their publications of the testimony of spurious experts whose reputations were made in literature, art or theology, and not in the service of healing. They must purge their propaganda of the fraud and trickery and evil insinuation that have for years characterized it. And I may perhaps be permitted to suggest that the process of making their methods

15. Grenfell, Wilfred T.: *A Voyage on a Pan of Ice*, Boston, 1908.

16. Published by the American Medical Association, Chicago. A list, with prices, appears on the second page of the cover of this pamphlet.

17. *The Will to Believe and Other Essays*, New York, 1899, p. 58.

clean and their ways straight involves paying some respect to the high purpose of biologic investigation and its beneficent achievements for human welfare, which together give meaning and sanction to the experimental use of animals.

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The Value of Animal Experimentation as Illustrated by Recent Advances in the Study of Syphilis

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BALTIMORE

DEFENSE OF RESEARCH PAMPHLET XX

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

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THE VALUE OF ANIMAL EXPERIMENTATION AS ILLUSTRATED BY RECENT ADVANCES IN THE STUDY OF SYPHILIS

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BALTIMORE

I. INTRODUCTION

No one who is alive to the nature of physical pain or aware of the charm of the domestic animals could fail to sympathize with an inquiry into the warrant for animal experiments. It has always seemed odd, it is true, that this critical demand should not only begin with, but often single out for its entire attention, the one human activity involving animal sacrifice which has for its aim the relief of human distress; and that the good souls who become so concerned over one etherized dog, can regard with indifference the packing industry—with its wholesale slaughter to appease appetite; or the fur industry—with its reckless massacres to satisfy vanity; or the fisheries—consigning myriads of helpless beings to slow death by drowning in the air.

Nevertheless, those who are responsible for deliberate experiments on animals recognize the request for its grounds of justification, as a perfectly reasonable one. If the discussion is one in which facts may be offered as evidence, it ought to be a simple matter to determine whether or not the achievements of the experimental method justify its continuance. The history of the subject is an open book; and in commending it to the honest inquirer, medicine need speak in no apologetic tone. Abundant facts for a final decision of the question would come to light through a study of bacteriology and surgical asepsis—a whole science based on experimentation; or of the acute diseases for which specific

cures have been determined (malaria, diphtheria, cerebrospinal meningitis); or of the plagues which may be absolutely prevented by hygienic and therapeutic measures (malaria, diphtheria, yellow fever, small-pox, rabies, tetanus); or of the hospital plagues which aseptic technic has almost abolished (erysipelas, blood-poisoning, hospital gangrene); or of the developments which have made every portion of the body accessible to surgery; or of the triumphs of obstetrics, which have reduced the appalling dangers of childbed fever to an almost negligible minimum. Even then only the most striking conquests of medicine would have been considered; and their significance would not have been even approximately grasped by those unfamiliar with the difficulties encountered by medicine at every step forward.

Nowhere, however, can the value of animal experimentation be so satisfactorily tested as in a study of the history of syphilis.

II. THE SOCIAL IMPORTANCE OF SYPHILIS

A just estimate of the value of animal experimentation in the development of the knowledge of syphilis is of vital interest because of the importance of the disease in the community. This is an importance usually overlooked by the public, whose interest is attracted by the more deadly plagues. Yet it is well within the limits of conservatism to say—so wide-spread is the disease, so calamitous and far-reaching are its effects—that none surpasses it, and few equal it in hygienic importance. The attitude of the public toward experimentation undertaken to extend our knowledge of this disease is then, obviously, by no means a matter of indifference.

Wide-spread as the disease undoubtedly is, we have no means of determining its exact extent with accuracy; so many cases go unreported, and so many of the late effects of the disease unrecognized, that all our estimates are underestimates. Yet even so, the figures are sufficiently striking. LeNoir, after a study of nine years, reported at the International Congress in Brussels that between 13 per cent. and 15 per cent. of the male adults of Paris were syphilitic; in other words, that in this city alone, and considering only the male sex, there were 125,000 cases of the disease. These figures were con-

firmed by Fournier;¹ yet they by no means give even an approximate idea of the extent of the disease, for they take no adequate account of the ravages of late hereditary and parasyphilitic processes.

Syphilis in its acute stages is not a frequent cause of death; and examination of mortality statistics would, therefore, hardly be expected to demonstrate the extent of its ravages—as it might be expected to do, for instance, in the case of typhoid fever. Yet some idea of its spread and significance may be obtained by a consideration of the attitude of insurance toward it. Runenberg² found that, including certain apoplexies, probably syphilitic in origin, the mortality from the disease was about 15 per cent.—the total being second only to that of tuberculosis which caused 21 per cent. of the deaths. These figures, which may be somewhat higher than other statistics would justify, assume added importance when it is remembered that they represent the facts existing among the insured, that is to say, the most vigorous, portion of the population. The damage done by the disease consists largely in its lowering the standard of average health, paving the way for other diseases and possibly laying the foundation for mental degeneration and alienation. The extent of these secondary effects can only be estimated. Most insurance companies require that four or five years shall have elapsed after the disappearance of the last symptoms of the disease; and no applicant who has had syphilis is given a policy which will keep him on the company's books after his fifty-fifth year. Greene³ goes even further, and firmly believes insurance at ordinary rates (even after an interval of five years) to be an error. Under no circumstances would he advise a straight life policy to be issued to a man who has a syphilitic history.

III. SYPHILIS IN THE ARMY

Consider the state of affairs in national organizations in which men are under constant discipline and something like accurate statistics may be obtained. Table 1 represents the admission-rate per 1,000 of strength for syphilis among the British troops in India.

1. Fournier: *Treatment and Prophylaxis of Syphilis*, Marshall's translation, edition 1906, Part II, p. 157.

2. Osler and Churchman: Chapter on Syphilis, Osler's Modern Medicine, iii, 495.

3. Greene: *Examination for Life-Insurance*, p. 118.

TABLE 1.—SYPHILIS AMONG BRITISH TROOPS IN INDIA PER 1,000 OF ADMISSIONS

Year.	Primary Syphilis, Inc. Soft Chancre.*	Secondary Syphilis.
1887	142.1	29.4
1888	142.1	32.4
1889	225.1	51.2
1890	220.7	66.3
1893	213.6	61.6
1894	248.1	74.6
1895	239.0	84.9
1896	226.4	97.7
1897	201.7	101.9

*It must be observed that the figures in this column include certain non-syphilitic venereal lesions. The above table is from French: *Syphilis in the Army*.

It is the study of such figures as these which leads experts like Sir Alfred Keogh⁴ to write:

It may be stated without fear of contradiction, that there is no disease, with the possible exception of malaria, that has so important an influence on the efficiency of an army or navy as syphilis. Other diseases doubtless are more deadly and consequently attract more attention; no other is so lasting in its effects, or so persistent in its attack on the bodily strength of the man who has once acquired it. A soldier gets enteric fever and either dies or recovers. Out of a hundred such, it may safely be prophesied that eighty will survive, and of these seventy, at least, be not only none the worse for their experience, but eventually all the more efficient for field-service in consequence of it. . . On the other hand, thirty men get syphilis, and not one of these can ever be considered the man he was before.

With this expert opinion in mind, a glance at the accompanying chart will convince any one of the tremendously crippling power of syphilis in an army. It represents the facts for the British army at home and abroad.

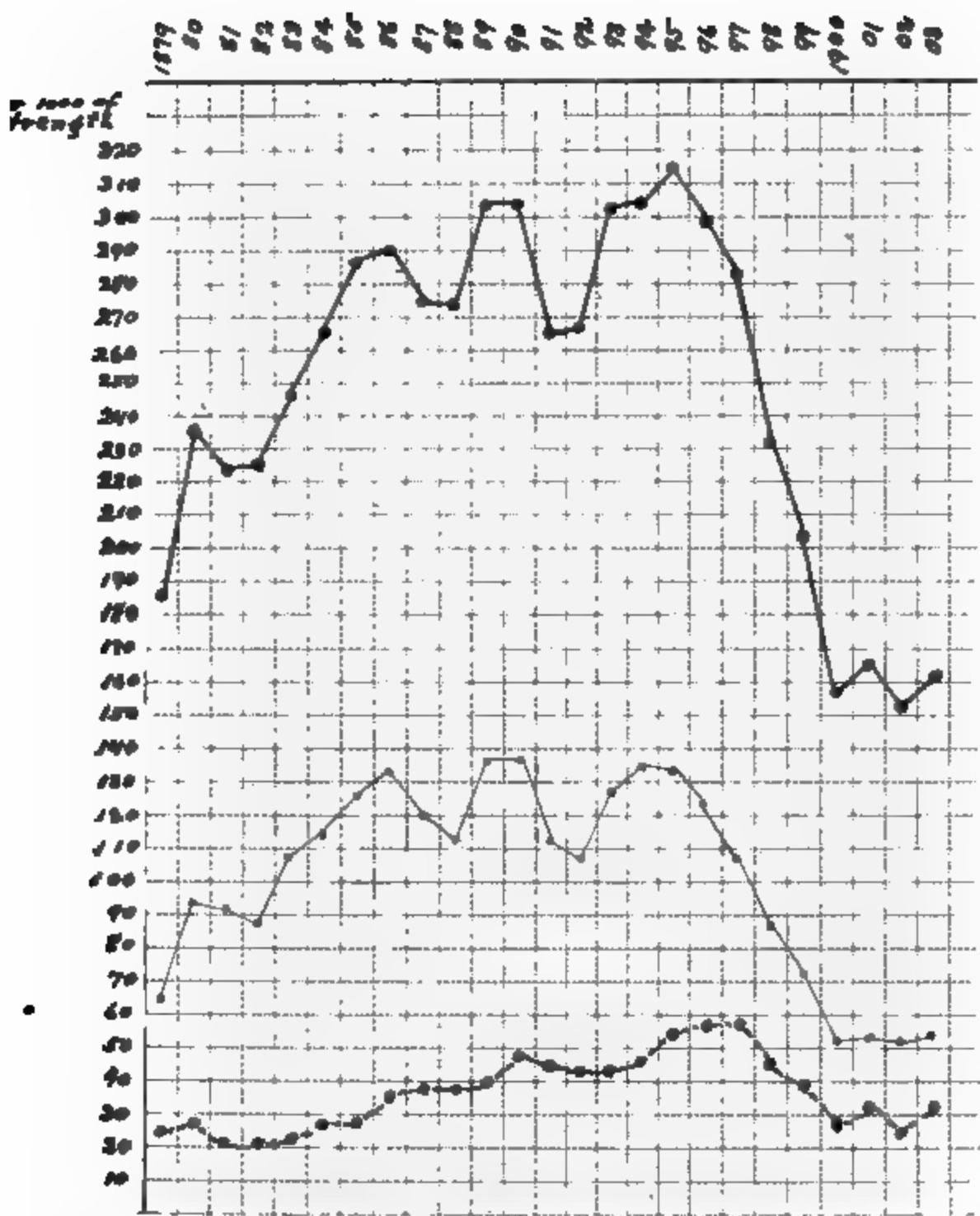
These statistics may be supplemented by two further tables, showing the incidence of syphilis in the armies of Great Britain and the United States.

TABLE 2.—THE INCIDENCE OF SYPHILIS.* THE BRITISH ARMY AT HOME AND ABROAD

Year.	Strength.	Admissions for Syphilis.	Admissions Per 1,000 of Strength.
1894	203,469	27,436	145.01
1895	200,681	28,081	140.41
1903	282,182	12,668	52.31
1904	244,425	9,219	37.72
1905	240,075	7,039	29.32
1906	230,128	5,958	25.89
1907	217,844	5,033	23.11
1908	215,647	4,137	19.19

*The slight discrepancies between figures in this table and those in the previous chart are apparently due to the fact that in the chart a certain small number of non-luetic lesions are included under "primary venereal sores." Tables 2 and 3 are from D'Arcy Power and Murphy: *System of Syphilis*, Volume VI.

4. Keogh: *Introduction to d'Arcy—Power and Murphy's System of Syphilis*, vol. vi.



Chart, taken from French *Syphilis in the Army*, Chart III, Appendix III. The upper, heavy line represents the incidence of all venereal disease; the middle, fine line represents the incidence of primary venereal sores; the lower, dotted line represents the incidence of secondary syphilis.

TABLE 3.—THE OCCURRENCE OF SYPHILIS IN THE ARMY OF THE UNITED STATES

Year.	Strength.	Admissions for Syphilis.	Admissions Per 1,000 of Strength.
1903	71,679	1,676	23.36
1904	59,671	1,525	25.56
1905	55,619	1,953	35.11
1906	53,573	1,869	34.89
1907	53,249	1,534	28.80
1908	50,705	1,436	28.32
1909	62,263	1,592	25.57

Syphilis is thus seen to be one of the most important causes of military inefficiency, even under the best conditions of medical supervision. Given the least leeway it may break out to an appalling extent, as it did among the British troops in the Peninsula, who christened it the "Black Lion of Portugal."⁵

IV. THE SERIOUS NATURE OF SYPHILIS

The wide incidence of syphilis is, then, sufficiently evident. But the great menace of the disease, not only to the two arms of the national defence, but to the health—even to the existence—of the nation as a whole, can be made plain only by a consideration of the calamitous nature of its clinical manifestations.

1. *Danger to the Individual.*—The dangers of the disease to the afflicted individual himself are perhaps roughly appreciated, though it is doubtful if the serious handicap to work, which the compromising and disagreeable secondary symptoms cause, is sufficiently understood. What is certain is that the laity and a majority of physicians wholly fail to appreciate the grave and often fatal nature of the tertiary manifestations. These are particularly pathetic, because they may appear in the prime of life, years after the initial lesion has been forgotten as a thing of the past; and may absolutely incapacitate an otherwise healthy man, who has become involved in the responsibilities of a husband and father. Nothing is more distressing than the sinister predilection of tertiary syphilis for the nervous system. Of 5,749 syphilitic patients studied by Fournier,⁶ 758 developed syphilis of the brain, and 1,099 others syphilis of the cord and nerves. That is to say, nearly one out of every three of the patients exhibited syphilis of

5. Ricord: Illustrations of Syphilis. Historical introduction in Belton's Translation.

6. Practically all that is here written on the dangers of syphilis is taken from Fournier's Treatment and Prophylaxis of Syphilis. Marshall's Translation, ed. 1906, a book that should be familiar to everyone interested in the disease and its relation to society.

the nervous system. And if to the multiform manifestations of the disease in its active stage be added the parasyphilitic phenomena — serious, incapacitating and as yet not amenable to treatment — some faint idea may be gained of the far-reaching effect of the disease on the individual.

2. *Danger to the Family.*—But it is as a menace to the family that this disease appears most formidable. No catastrophe can be more disastrous than its spread by the marital relation; no spectacle more dreadful than its transmission to innocent children.

It is the wife, of course, who is most often—though not *always*—innocently infected; and when this occurs, disasters of many kinds follow. The woman herself is submitted to the discomfort, the risk and the degradation of syphilis; and no consequence of the disease can be more distressing. Nor is this occurrence a rare one. Those who regard syphilis as the peculiar property of the underworld, and eye its victims with suspicion, would be surprised at the facts brought out by Fournier⁶ who, in a study of 100 syphilitic women, found one in every five to have been innocently infected by her lawful husband. Such a woman must suffer not only in her own body; she must expose her children to the most serious form of syphilitic heredity—mixed heredity. It is only natural that such a train of affairs once started often ends in the dissolution of the family. Even if actual divorce does not ensue, the family ties fail to stand the test; affection and respect die; and we have the melancholy spectacle of a house divided against itself. Moreover, not infrequently, economic ruin ensues through incapacitation of the head of the family and the household becomes a public burden.

3. *Danger to Posterity.*—But this foul disease appears most foul in its dastardly attacks on the second and third generations; and all other features fade beside its importance in heredity. Indeed, the need of protecting innocent children from syphilitic infection is the complete answer to those who object to the removal of the consequences of syphilis as inciting to vice.

An infant mortality astonishingly high is what the disease produces. In many instances this amounts to a complete annihilation of posterity. Ninety women studied by Fournier—all seen in private practice, all of good constitution and surrounded by a favorable environment

of hygiene and wealth—became pregnant during the first year of the disease ("the year of terror"). Fifty of these women aborted, thirty-eight infants died soon after birth, and only two children survived—a mortality of 97.7 per cent.! Another study included 200 men who had married while syphilitic, but who failed to contaminate their wives. Four hundred and three pregnancies for which these men were responsible resulted in 288 living children and 115 still-births, abortions and early deaths. Instances of excessive infantile mortality could be indefinitely multiplied. Ribemont-Dessaaignes, for instance, reports a woman who contracted syphilis from her husband; she became pregnant nineteen times, had five still-births and gave birth to fourteen children, every one of whom died under 6 months of age. "A child," writes Fournier, "conceived by a woman in the course of recent syphilis is almost certainly condemned to death."

But to this dreadful indictment must be added the woful heritage which syphilitic parents bequeath to the children who do manage to survive. Fragile infants—a prey to every infection; monsters; pathetic and wizened mannikins; idiots; normal children, condemned to a late syphilitic heredity at the second dentition or at puberty—this is the spawn of syphilis. Nor does the trail of the beast stop here; the heritage which these unfortunates receive they pass on to their descendants; and the effects of the disease in heredity may be traced through three generations (Gilbert, Caubert, Étienne). "To cleanse the brothel," writes Fournier, "is not only to protect those who frequent it; it is also to protect the family hearth, the honest woman, the child and the race."

That syphilis is a formidable national scourge and that complete knowledge of it is of fundamental hygienic importance may, then, be regarded as established.

V. KNOWLEDGE OF SYPHILIS GAINED BY THE EMPIRICAL METHOD

We have next to inquire into the state of medical knowledge of the disease before animal experimentation began. This will be particularly instructive; because by comparing the knowledge thus slowly acquired, through long years of simple observation, with the rapid advances made in the few years in which the study of the disease

by the experimental method has been possible, we get a vivid picture of what productive animal experimentation, now adding daily to our knowledge of syphilis, really means.

It may be said at once that the information about syphilis which medicine was able to accumulate, entirely without the aid of animal experiment, was marvelously complete and accurate. Here is a disease, protean in its manifestations, affecting probably every organ in the body, pursuing a long and insidious course, almost identical in its initial forms with other simple venereal infections and possessing a peculiar power of mimicry, whereby it can simulate minutely the signs and symptoms of numerous other diseases. The conditions could hardly present greater difficulties. Yet, purely by the method of clinical observation, chaos was gradually reduced to order. It is true that this result was many long years achieving. At the time of the European syphilitic pandemic (1494) enormous confusion prevailed as to the nature of the various venereal infections. The difficult problem was gradually solved—but how gradually, may be realized when it is recalled that not until nearly 400 years had elapsed was the question of the dualistic nature of syphilitic and non-syphilitic venereal infections settled.

Quite as interesting as the completeness of the clinician's acquaintance with syphilis in pre-experimental days, was the satisfactory condition of its therapeutics. Working by purely empirical methods and entirely without a rational or an experimental basis, the early physicians found and developed a method of treatment by which the disease could almost always be controlled, and, in a large majority of cases, absolutely cured. The choice of mercury—recommended in syphilis by the Galenists for the most absurd of reasons—happened to be a lucky guess.

In 1836 the administration of potassium iodid in syphilis was recommended by Wallace. This date is an important one in the history of the disease: for it does more than mark the year of a valuable contribution to therapeutics. It marks, too, the end of important advance in our knowledge of the disease; for from that year until the recent successful experimental work on animals, medicine stood practically still so far as syphilis was concerned. A few advances were, of course, made;

the debate as to the dual nature of luetic and non-luetic lesions was brought to a conclusion by the French school (Bassereau, Fournier, Clerc, Ricord); certain unrecognized syphilitic lesions were described (arthropathies by Richet, bursopathies by Verneuil); extensive statistical studies were made by Fournier and others; and the importance of parasyphilitic and late hereditary forms was recognized and emphasized. But no really new light was thrown on the disease. Clinical study had about reached the limit of its possibilities.

VI. DEFICIENCIES IN PRE-EXPERIMENTAL KNOWLEDGE OF SYPHILIS

It is essential for one interested in good faith in determining the value of experiments on animals in syphilis to ask whether there was any need that this intimate, and in many respects, satisfactory clinical and therapeutic knowledge be supplemented by facts which animal experimentation might supply. Was it merely that scientific curiosity craved satisfaction? Or were there real hygienic needs to be met, and to be met only by the study of the disease in animals?

That a vital demand for further knowledge existed becomes at once apparent when it is stated that, complete as our knowledge of syphilis was, there were a number of points at which it was replaced by ignorance as complete; and that this ignorance concerned certain fundamental features of the disease.

In the first place, it has often been impossible to make an early diagnosis. The first sign of syphilis (the chancre) usually appears about three weeks after infection has occurred. When it *does* appear its nature is often so uncertain that further phenomena must be awaited before the prolonged and disagreeable treatment can be instituted. If specific treatment is undertaken immediately, the sore will disappear, secondary symptoms may never present themselves, a positive diagnosis may never be made and the treatment—which, to be effective, must be carried on thoroughly over a period of years—will at first be half-heartedly undertaken and in a short time discontinued. On the other hand, if treatment is not promptly begun, valuable days, even weeks, pass before the disease can be positively recognized and attacked.

In the next place, positive diagnosis in the later stages of the disease is often impossible. Those unfamiliar with the protean manifestations of syphilis have no conception of the difficulty it may present in diagnosis. Even the most experienced physicians are often unable to tell whether a given condition is syphilitic or not.

But a graver deficiency in our knowledge of this disease, is our inability to recognize it in its "latent" forms. In these cases the infection, though still present and likely to break out at any time or to be passed on to others, is not at the moment producing any obvious signs or symptoms. It is this form of the disease which contributes largely to the danger of syphilis among prostitutes; for the existence of latent syphilis, though a real menace to the community, may escape the most careful medical inspection. A syphilitic woman could quite well be the source of widespread infection and yet possess a clean bill of health on the absence of obvious signs.

Moreover, we have never known how long it was necessary to continue treatment before a complete cure was obtained. As our knowledge of the disease advanced, it became clear that a longer and longer duration of treatment was necessary for safety; and it is now rather arbitrarily estimated at about three years. But this is only an estimate. And how unsafe it is to proceed, in this matter, on an estimate becomes apparent when the importance of the disease to marriage is borne in mind. All physicians are agreed that no syphilitic should marry until the disease has been positively cured; but they have no way of telling just when cure has been effected; and have, therefore, always lacked the necessary data for intelligent advice to their patients.

Finally, so long as the cause of the disease was unknown and the possibility of its study by the methods of reproduction in animals excluded, advances in the knowledge of the disease—such as these methods had made possible in the case, for example, of suppuration—were quite out of the question.

VII. WHAT EXPERIMENTAL RESEARCH HAS ACHIEVED IN THE CASE OF SYPHILIS

1. *Successful Reproduction in Animals.*—Previous to 1903 animal experimentation practically did not exist so far as syphilis is concerned. So many of the attempts to transmit the disease to animals had been unsuccessful,

and so difficult was it to control the supposedly successful results, that the general attitude toward the subject was one of apathy. Certain observers had indeed reported successful transmission to animals. Auzias-Turenne,⁷ for example, claimed to have inoculated the cat; LeGros and Lancereaux,⁸ the pig; and an occasional success had been obtained in monkeys (Klebs,⁹ Martineau and Hamonic,¹⁰ Nicolle¹¹ and others). But the successes had been only occasional and could not be substantiated by independent observers.

In 1903, however, the first communication of Metchnikoff and Roux¹² was published by the Pasteur Institute. The authors reported the undoubtedly successful transmission of syphilis to a two-year-old female chimpanzee; and the equally successful inoculation of a male chimpanzee with material taken from the first animal. Several bonnet monkeys (*M. sinicus*) were also successfully inoculated; but certain species (e. g., the mandrils) seemed to be insusceptible. These experiments were promptly repeated by Lassar¹³ and the results confirmed.

The successful inoculation of animals immediately opened up a dozen avenues of research, and a second communication soon appeared from the same workers:¹⁴ Here, continuation of the inoculation experiments was reported; and it was apparently demonstrated that monkeys might be divided into two groups, according to their susceptibility to syphilis—the anthropoids approaching the lower races of man in susceptibility, the mandrils and maimons exhibiting a complete natural immunity to the disease. The idea was therefore confirmed, which had previously been advanced by others, that failure to use susceptible animals probably explained much of the inconsistency of the experimental work done before this time. Additional confirmation of this work soon came from Neisser,¹⁵ who reported successful inocu-

7. Auzias-Turenne: *La syphilisation*, 1878, p. 422.

8. Legros and Lancereaux: In *Dictionnaire Encyclopédique des Sciences Médicales*, 1884, xiv, 498.

9. Klebs: *Arch. f. exper. Path.*, 1879, x, 161.

10. Martineau and Hamonic: *Bull. de l'Acad. de med.*, 1882, 1007; *Soc. med. des hôp.*, 1883; *Rev. Clin. d' androl. et de gynécol.*, 1903, p. 225.

11. Nicolle: Not published; quoted by Metchnikoff and Roux in their first communication.

12. Metchnikoff and Roux: *Ann. de l'Inst. Pasteur*, 1903, xvii, No. 12.

13. Lassar: *Berl. klin. Wchnschr.*, 1903, No. 52, p. 1; 1904, p. 801.

14. Metchnikoff and Roux. *Ann. de l'Inst. Pasteur*, 1904, xviii, No. 1.

15. Neisser: *Deutsch. med. Wchnschr.*, 1904, pp. 1369, 1431.

lations of chimpanzees, orang-outangs and a gibbon. In 1904, Metchnikoff and Roux's third communication¹⁶ appeared. Here the particularly interesting point was made that the syphilitic virus would not pass through a Berkefeld filter. Klingmüller and Baermann¹⁷ had previously made the same assertion *after having inoculated themselves with human syphilitic material* which had been passed through a Berkefeld filter. Finally, the two workers at the Pasteur Institute published their conviction, in a fourth communication,¹⁸ that the chimpanzee, by reason of its susceptibility to syphilis and the similarity of the symptoms produced with those seen in human beings, was the most suitable animal for experimental purposes. More important still, they were able to confirm the work of Schaudinn, which had meanwhile appeared, by finding the *Spirochæta pallida*¹⁹ in 74 per cent. of thirty-one syphilitic monkeys. Thus did the two lines of research promptly cross.

Experimental work on animals other than monkeys was never very conclusive until Bertarelli²⁰ reported the successful inoculation of the cornea in rabbits. A similar result had been obtained by Haensell;²¹ and Bertarelli's observations were promptly confirmed by Hoffmann and Brüning,²² by Scherber,²³ and by Greef and Clausen.²⁴

Thus, in a few short years the technic of animal experimentation—so fruitful in other fields—has been developed for syphilis. It is impossible to exaggerate the importance of this advance, which touches the whole dreary prospect of syphilis with hope. The work of Metchnikoff and Roux on susceptibility and immunity, of Finger and Landsteiner²⁵ on the infectiousness of tertiary lesions and of semen, of Neisser on the syphilitic testicle: these are a few instances of the way in which new avenues of progress were immediately opened up

16. Metchnikoff and Roux: Ann. de l'Inst. Pasteur, 1904, xviii, 657.

17. Klingmüller and Baermann: Deutsch. med. Wchnschr., 1904, p. 766.

18. Metchnikoff and Roux: Ann. de l'Inst. Pasteur, 1905, xix, 673.

19. There is some disagreement as to the proper name for this organism. *Treponema pallidum* is probably more correct, but *Spirochæta* is used here as being more familiar.

20. Bertarelli: Centralbl. f. Bakt., Orig. 1, 1906, xli, 320.

21. Haensell: Arch. f. Ophth., 1881-3, xxvii, 93.

22. Hoffmann and Brüning: Deutsch. med. Wchnschr., 1907, No. 14, p. 553.

23. Scherber: Wien med. Wchnschr., 1906, p. 726.

24. Greef and Clausen: Deutsch. med. Wchnschr., 1906, p. 1454.

25. Finger and Landsteiner: Arch. f. Dermatol. u. Syph., 1906, lxxviii, 385; lxxxi, 146.

and promptly traveled by eager scientists. The prevention of syphilis, which previously seemed an utopian dream, became—once the transmission of the disease to animals was assured—a reasonable, if remote, hope; and there was not a single dark crevice into which this discovery did not throw encouraging light.

2. *Discovery of the Cause of Syphilis.*—The year 1905 marks the beginning of a new era in the history of syphilis; for a publication which then appeared put an end to the long and weary search for the cause of the disease. The idea of a living contagium in syphilis had long been held, and the tale of the search for it is one to make the judicious grieve. But a new light broke with the appearance of the paper of Schaudinn and Hoffmann.²⁶ It was an epoch-making report, but it was a model of calmness. Despite the importance of the observations, the facts were cautiously stated and a discussion of their significance postponed until the accumulation of further data. The authors had found, they said, a characteristic, non-refractile, delicate organism, 4-14 microns in length, pointed at both ends, with numerous clear, tight, corkscrew-like spiral curves. It was readily distinguishable from other bacterial and protozoan forms, and had been found in numerous primary and secondary syphilitic lesions. Moreover, Metchnikoff had been able to demonstrate its presence in the primary lesion of an experimentally inoculated ape.

This paper immediately awakened a new interest in the subject throughout the world; and confirmatory evidence soon accumulated in enormous amounts.²⁷ Before long, what had at first been cautiously accepted as a probability bordering on certainty, became a certainty; the *Spirochæta pallida* of Schaudinn and Hoffmann withstood all efforts to disprove its etiologic relation to syphilis; and the long and weary search for the cause of the disease was at an end.

3. *Discovery of a Diagnostic Reaction Specific for Syphilis.*—Hardly less important than the discovery of the cause of syphilis, was the demonstration of a biologic

26. Schaudinn and Hoffmann: Arb. a. d. k. Gesndhtsamte, xxii, No. 2, p. 527; Deutsche med. Wchnschr., 1905, No. 18, p. 711.

27. It is impossible to indicate even the more important articles. The early literature on the *Spirochæta pallida* is collected in a Leipsic thesis by Julius Glass, December, 1905; and by Herxheimer, in Lubarsch and Ostertag's *Ergebnisse der Alleg. Path.*, Jahrgang, xi, Abteil. 1. The article by F. P. Gay in Internat. Clin., 1907, iii, series 17, p. 199, is accompanied by a useful bibliography.

reaction, the presence of which is absolute proof of the existence of the disease, even in the absence of signs or symptoms.²⁸ The very great value of such a reaction in cases of doubtful diagnosis, and particularly in latent syphilis, needs only to be mentioned to be appreciated. The reaction was discovered almost simultaneously by Wassermann, Neisser and Bruck,²⁹ and by Detre,³⁰ working independently, but with practically the same technic. The names of Bordet and Gengou³¹ must, however, be borne in mind in this connection. These two pioneer observers (who also recognized the *Spirochæta pallida* before Schaudinn and just missed appreciating its significance) were the first to describe the general phenomenon of complement fixation (or deviation), of which the Wassermann reaction for syphilis is a modified example. *This highly theoretical investigation and the immensely practical application of it by Wassermann depended on animal experimentation at every step.*

The Wassermann reaction depends on the capacity which the serum of syphilitic patients has to fix complement in the presence of extracts of syphilitic tissue, or certain other alcoholic extracts. This fixation of complement is tested for by the use of a so-called hemolytic system, which consists of red blood-cells, and a serum capable, in the presence of complement, of hemolyzing them. It is impossible to define the reaction without the use of highly technical terms which would themselves require extensive definition. Here, one may simply state how the test is made. Extract of known syphilitic material and the blood-serum of the patient to be tested are mixed in a test-tube. Fresh guinea-pig serum is then added and the mixture incubated to allow complement-fixation to occur. The hemolytic system, which requires complement for the completion of the hemolysis, is next added. If the serum to be tested is not syphilitic, complement is not bound and hence is available for the

28. The reaction has been observed also in leprosy and in scarlet fever; but for practical purposes these exceptions do not impair its diagnostic value.

29. Wassermann, Neisser and Bruck: Deutsch. med. Wchnschr., 1906, xxxii, 745; Wassermann, Neisser, Bruck and Shucht: Ztschr. f. Hyg. u. Infektionskr., 1906, iv, 451; Wassermann: Wien. klin. Wchnschr., 1906, xxi, 745; Wassermann and Meier: Deutsch. med. Wchnschr., 1907, xxxiii, 1287.

30. Detre: Wien. klin. Wchnschr., 1906, xix, 619; Detre and Brezovski: Wien. klin. Wchnschr., 1908, xxi, 1700.

31. Bordet and Gengou: Ann. de l'Inst. Pasteur, 1901, xv, 289; Bordet: Bull. de l'Acad. royale de Belgique, 1906, xx, 454; Ztschr. f. Immunitäts-Forsch., 1909, Referate I, 1. Bordet and Gay: Ann. de l'Inst. Pasteur, 1906, xx, 467.

use of the hemolytic system; hemolysis, therefore, proceeds, the red blood-corpuscles continue to be destroyed, the mixture becomes red in color and the test is negative. If, on the other hand, the serum is syphilitic, complement is bound, hemolysis inhibited, the red blood-cells not destroyed, the mixture not reddened, and the test is positive.

This test, while not absolutely constant, has turned out to be one of the most valuable of the biologic reactions. When the test is negative, syphilis is not excluded; but when positive, a diagnosis of syphilis is to be made with almost absolute certainty. It has already shown itself even more reliable than the Widal reaction; and no one familiar with typhoid fever is ignorant of the very great value of this diagnostic test.

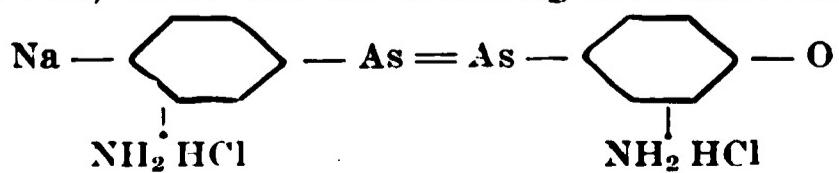
4. *Discovery of a Specific Drug for Syphilis.*—It would be difficult to find in the history of medicine a more interesting and instructive story than the account of the work which led up to the discovery of salvarsan (606). When Ehrlich began his work years ago, syphilis was the last thing in his mind. He was interested at that time in the idea which possessed him that every living cell has a chemical affinity for some particular substance. This property of mutual attraction he called chemotropism; and in experimenting with dyestuffs he came upon a very pretty example of it in the selective affinity which methylene-blue exhibits for cells of the nervous system. If, then, such a specific affinity did exist, it seemed quite probable that it might also exist between certain drugs and certain parasites; and after some years of further experimentation Ehrlich was able to investigate this point. He believed that for each specific parasite, a specific curative drug could and would be found.³² Because of the sleeping-sickness epidemic in Africa and because the disease is easily transferable to mice, Ehrlich began with a study of this affection. He succeeded, in connection with Weinberg, in producing a new dyestuff (trypan-red) which caused the organisms to disappear from experimentally inoculated mice in one injection. It was soon shown that parasites rapidly acquired a tolerance for such drugs and that, in order permanently to cure a parasitic disease, it was necessary to destroy every single parasite in the

32. Marks, L. H.: Ehrlich's Biochemical Theory. Its Conception and Application, THE JOURNAL A. M. A., Dec 3, 1910, p. 1974.

shortest possible time. Ehrlich's very difficult problem then became to produce a substance which was so specific for given parasites as completely to destroy them at one injection, but which was at the same time harmless to the infected animal itself. Starting, then, from atoxyl—an arsenic compound known to be efficacious in trypanosomiasis, but dangerous to the animal—Ehrlich proceeded to the solution of the problem. The task was one of colossal dimensions. Hundreds of substances had to be synthetized and then tested for toxicity on various species of animals. Of the large number of drugs made and tried, only about ten stood the test.

At about this stage in the work it was shown by Bertarelli and others, that syphilis could be transferred to rabbits; and Ehrlich turned his attention to the diseases caused by the spirilla and spironema: syphilis, relapsing fever and chicken spirillosis. In a short time a drug was produced—No. 606 in the series—which Hata found would definitely cure chicken spirillosis in a small, safe, dose, would completely sterilize a mouse infected with relapsing fever, and—in a dose one seventh of the *dosis tolerata*—was sufficient to cause the *Spirochæta pallida* to disappear from a syphilized rabbit.³³ Ehrlich repeated the experiments; the drug was again tested on dogs, and on two of Professor Alt's assistants, who volunteered to demonstrate in this way the safety of the drug for human beings. It was then tried on patients. In order to make the test of the drug on human beings as convincing as possible, Ehrlich distributed 20,000 doses to clinicians of standing throughout the world, on the condition that certain rigid restrictions in administration be observed, and that the patients be kept in hospitals several days for observation. On the results thus obtained, Ehrlich will base his conclusions as to the value of the drug in the treatment of human syphilis. Those who have attempted to assemble, one at a time, 20,000 objects of any kind—say something as readily accessible as a canceled two-cent stamp—will appreciate something of the magnitude of this task, when they remember that the preparation of the dose of the drug,

33. The chemical name of this preparation is p.p.—dioxy—m.m.—diamido-arseno-benzol. It is used in the form of hydrochlorid of the sodium salt, which has the following structural formula :



the necessary examination and subsequent observation of the patient, the preparation of the records, the critical examination of the results—are proceedings which represent hours of work for each individual case; and that this colossal task is merely the final stage in a research which has been going on for years. This point is worth calling to the attention of those who are accustomed to regard animal experimentation as child's play, undertaken at odd moments, by brutes who love to see animals squirm.

This account of the work of Ehrlich is the briefest possible sketch.³⁴ It conveys no idea whatever of the difficulty of the problems attacked, or of the genius displayed in overcoming them. It says nothing of several important contributions made to the theory of science, and to the practice of medicine, by the way. One of the earliest points brought out, for example, was a demonstration of the true chemical nature of atoxyl. Again, trypan-red—though used by Ehrlich against sleeping-sickness—was shown by Nuttall to be also effective in the widely distributed Texas fever of cattle. Salvarsan (606), sent by Ehrlich to Iversen in Russia, proved to be of very great value in the treatment of relapsing fever.

Of the exact value of the drug in syphilis it is too early to speak; the evidence is not yet all collected and has not been made public. Moreover, it is recognized as quite possible that a drug so powerful may have important deleterious effects; and until this point is cleared up by experience, any judgment as to its final place in medicine is ill-advised. It is, however, an open secret that astonishing results have been obtained. From the clinics of Wechselmann and many others, reports have already appeared which make it seem certain that—even if the final results fail to fulfil the early hopes—a contribution of the very first importance has been made to the therapeutics of syphilis.

But Ehrlich's work has been more than a contribution of this sort. He has founded a new science of chemotherapy, and has given a new vitality to pharmacology—hitherto interested largely in the toxic effects of drugs on normal animals. He prophesies a new era to be brought about by the interest of chemists like Baumann and Emil Fischer, and clinicians like von Mehring in

34. Marks, L. H.: Paul Ehrlich; the Man and His Work, McClure's Magazine, December, 1910; Schweitzer: Ehrlich's Chemotherapy—a New Science, Science, Dec. 9, 1910.

practical therapeutics. "On the basis of years of experience in the laboratory," he writes, "I indeed believe I am justified in expressing the hope that, by carefully following the path [of chemotherapy] which I have sketched, a sure advance will be made."³⁵ These are the cautious and serious words of a serious man, whose talent and achievement place him in the very first rank. It is the opinions of such men which should be decisive in these matters.

This, then, is what animal experimentation has done for syphilis. In a period of about seven years the cause of the disease has been established, a specific reaction for its detection has been discovered, its successful transmission to animals has been accomplished, and a drug of apparently first-rate importance has been advanced for its treatment. Those who make practical achievement the final test of the value of experimental work, could hardly ask for more convincing evidence than these splendid results provide.

VIII. PRACTICAL VALUE OF RECENTLY ACQUIRED KNOWLEDGE OF SYPHILIS

To appreciate, however, the real significance of these advances it is necessary to do something more than merely state them. No one could possibly deny their importance, regarded simply as achievements. But it is conceivable that this might not be regarded as sufficient justification for them. "Do they," it might be asked, "represent merely the triumph of scientific curiosity over great natural obstacles; or have they really made medicine more efficient, by enabling it to deal better with this disease?"

It must, in reply, be at once stated, and stated with great emphasis, that there is not a single weak point in the medical attack on syphilis which recent animal experimentation has not strengthened; that complete knowledge has in many places replaced complete ignorance; that diagnosis has been made easy where it was previously difficult, and possible where it was previously out of the question; that the efficiency of treatment has been tremendously increased; and that the way has been indicated for the solution of many, if not all, of the difficulties which still remain.

35. Ehrlich: Ber. d. deutsch. chem. Gesellsch., xlvi, No. 1.

In order to justify these extreme claims let me take up, in an itemized way, the deficiencies in our previous knowledge, which have already been indicated, and apply to them the facts which animal experimentation has supplied.

1. *Possibility of Early Diagnosis.*—An early diagnosis of syphilis is now possible. On the appearance of the initial lesion, we are able—by finding the recently discovered *Spirochæta pallida*—to make a positive diagnosis of the disease. The confusion with non-syphilitic genital lesions has become a thing of the past and it is no longer necessary to waste valuable time awaiting the appearance of secondary symptoms before treatment is begun.

2. *Increased Possibility of Positive Diagnosis.*—A positive diagnosis is now possible in many cases which previously went unrecognized. The Wassermann reaction and the demonstration of the *Spirochæta pallida* are of great importance in making the sometimes difficult differential diagnosis between syphilis and the host of affections which may simulate it—a diagnosis which, without these aids, was often simply not made.

3. *Recognition of Latent Syphilis.*—It is now possible, in a large majority of cases, to recognize "latent" syphilis. Heretofore, unless symptoms recognized as definitely syphilitic were present, we had no means of detecting the disease. Now, it is possible to say not only that a man has syphilis, but (in a fairly large proportion of cases) that he has had it. This is an advance of the very greatest importance. It enables us to recognize the syphilitic nature of many affections which might otherwise be badly treated. And it promises to be of value in the solution of the vexed problem of prostitution; for we are now able to tell, with a good deal of exactness, which prostitutes are infectious, and efficient hygienic control becomes a possibility. Indeed, the means for the detection of the disease in the absence of symptoms, the means for its positive diagnosis, and the means for its cure, having been provided, it is now possible for the community—if it choose to make intelligent use of the knowledge—to rid prostitution of syphilis. And this means, in time, the abolition of the disease from the face of the earth. If this sounds like an utopian dream, one has but to recall small-pox, which once raged everywhere, but which medicine—with slender means at her disposal—finally overcame. Sufficient knowledge is now

at hand to enable us to recognize and control the main foci of infection; proper use of this knowledge will eradicate syphilis, even though prostitution itself continue, as it quite well may, to flourish.

4. Possibility of Ascertaining a Definite Cure.—The time when a syphilitic patient may be regarded as cured, and not only free from the disease himself, but incapable of transmitting it to others, may now be known with practical exactness. The importance of this fact in relation to the question of marriage is evident. To the syphilitic patient anxious to marry, but equally anxious not to confer on his future wife and children the dangers of the disease, medicine has heretofore been able to give only halting advice. After three or four years of treatment she has allowed him to marry, but always with some misgivings. Now, she will certainly forbid his marriage if his Wassermann reaction is positive, no matter how long he has undergone treatment, or how complete is his freedom from symptoms; and she will allow the marriage confidently, if the reaction becomes negative and remains so without treatment. Moreover, if the state ever finds itself prepared to exercise an enlightened control over the physically unfit to prevent them from passing their burdens on to posterity, medicine stands ready to indicate to the state just what, so far as syphilis is concerned, constitutes unfitness.

5. Proof of Infectiousness of the Tertiary Lesion.—Not least of the contributions of experimentation has been the proof of the infectious nature of the tertiary lesions. This fact has only to be stated for its importance to be understood.

6. Increased Activity with Regard to Syphilis.—Finally, now that the cause of syphilis is known and methods for its study in animals are at hand, the lethargy of preexperimental days, in regard to syphilis, disappears, and is replaced by enthusiastic and hopeful activity. For it must be remembered that the study of syphilis by the use of animals is yet in its infancy; that only the bare beginnings have been made. The recently acquired knowledge of the disease is still in a fluid state; and it is difficult to estimate exactly what the ultimate value of the observations made, will be—as difficult as to prophesy the exact future position of every boat in a fishing fleet, making for harbor with favoring wind and current. Yet, the wind that blows is the wind of prog-

ress; the current is the current of hope; and the haven ahead is the harbor of health. Behind, lies the troubled sea of chaos and despair. Anyone who thinks this a mere figure of speech is invited to consider the incalculable value of the achievements of recent experiments for the host of innocent women, menaced by this disease, and the great army of unborn children, threatened with a syphilitic heritage; and to recall that the loss of animal life involved in the work, shrinks to insignificance beside that represented in any meat market you choose to pass, while the amount of animal suffering entailed might easily be duplicated in every one of a thousand fisheries, to whose activities the "humane" societies give never a thought.

IX. SYPHILIS AND ANTIVIVISECTION

The importance of a consideration of syphilis in arriving at any conclusion as to the justification of animal experimentation has, I think, been made sufficiently clear. But a word should be said about the light thrown on one or two of the stock objections to animal experimentation by a consideration of the experimental investigation of syphilis.

It is often asserted that research should be so controlled and limited that only those lines of work could be followed which give reasonable promise of practical result; and that the repetition of experiments solely for the purpose of confirming the work of others, should be made impossible. This sounds like a reasonable suggestion. Yet see how fatal such a policy would have been to the development of the knowledge of syphilis.

The whole remarkable success of Schaudinn came during a research undertaken to confirm the observations of another. Siegel³⁶ had reported the constant finding of an organism (*Cytorrhycetes luis*) in syphilitic lesions; and the Imperial Board of Health of Berlin appointed Schaudinn—a highly trained protozoologist—to repeat the work and see if the observations could be substantiated. Siegel's findings were not confirmed, but during the investigation, the real cause of syphilis was unearthed.

Again, who could possibly have prophesied that Ehrlich's early interest in the chemistry of the dyestuffs would lead to contributions to the therapeutics of syph-

36. Siegel: München. med. Wehnschr., 1905, p. 1321.

ilis? If it was to have any valuable results, one would have expected them in the industrial arts. Yet, starting with chemistry, he then turns his attention to protozoan disease, finds the new science of chemotherapy, hears of the work of Schaudinn and Bertarelli, becomes interested in syphilis and ends by making an important contribution to its therapeutics. One is reminded of the career of Pasteur who began in physics, with the study of crystallography, was lead into an investigation of the wine and silk industries, founded the science of bacteriology and made a contribution to therapeutics of the first importance.

Indeed the work of the various students of syphilis has been so intertwined, and the results of one of so much value to the others, that in an account of any one research most of the prominent names appear and reappear. Schaudinn, Ehrlich, Metchnikoff and Roux, Siegel, Bertarelli—it was the constant familiarity of each of these with the work of the others, and the constant attempts to confirm and advance the results already obtained, that led to the marvelous progress made. Even so remote an event as the discovery of the coal-tars, years before, by Perkins, contributed to the result; for it made not only bacteriology, but also chemotherapy possible.

It is this interdependence of research and the property of discoveries to have the most remote and unexpected value that makes restriction to experimentation, based on the probable importance of its results, unwise. Those who have become familiar with the subject by actual work in the laboratories, feel that to add to the already great difficulties of experimentation, by surrounding it with petty restrictions, would be to reward medicine for her fine achievements by crippling her, to equip her for future tasks by veiling her eyes. For it must be remembered that it is after all to medicine, and not to the "humane" societies, that the public looks for relief from disease; and when your "humane" legislation has forced your scientist into exile if he is to continue his work of enlightenment (this is how Great Britain "encouraged" Lister!), who is to accept the high responsibility for increasing efficiency in the treatment of disease demanded by the suffering patients who will continue to crowd the hospitals? Will the "humane" societies, after making it a misdemeanor for a scientist to operate on an etherized dog without running to them for a permit, undertake to furnish us, in some other way

than by experimentation, with the sorely needed facts about cancer and other unconquered plagues? Or should this work be entirely entrusted to those who have proved their fitness by their achievements in the study of syphilis?

It is high time that some protest was made against the cowardly charge that animal experimentation brutalizes men; and time, too, that those who launch it ceased to attain thereby a reputation for high moral sense in the community. The facts in the case are readily accessible; and if the charge is made in good faith, it ought to be backed by a notorious evidence of brutality in the profession which authorizes, and is in sympathy with, this "brutalizing" work. But whatever else physicians, as a class, are, brutal—they most decidedly are not. Medicine can point to a group of heroes, not to be surpassed in any profession, who have testified to the sincerity of their scientific zeal by offering their own bodies as material for experiment; and until the opponents of animal investigation can match this, charges of brutality come from them with very bad grace indeed. Moreover, it is a simple fact that the physicians of any community—devoting their lives to the relief of distress—maintain a reputation for interest in others to which the term "brutal" is simply not applicable; and that in communities where experimentation is going on it is to those interested in animal investigation that the profession looks for leadership in its far-sighted campaign for the health and happiness of this and future generations. The reputation of these leaders, so far as brutality is concerned, is above reproach. The high standard of Pasteur, most kind-hearted of men, most active of experimentalists—has been maintained by his successors; and those who, in their righteous indignation, echo the outcry against experimentation on the ground of its brutalizing effect, might better serve the cause of righteousness by an inquiry, among the scientists in their own community, into the truth of this serious accusation.

If, however, this charge—so far from being made in good faith and on the basis of actual instances of brutalization of character by experiment—represents, for all its odor of piety, merely an academic makeshift for the purposes of debate, then one can but marvel at the moral standard of those who, in their concern over animals, permit themselves to make against a profession, busy with intelligent philanthropy, a charge so grave and so unjust.

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Animal Experimentation in Relation to Epidemic Cerebrospinal Meningitis

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BOSTON

DEFENSE OF RESEARCH PAMPHLET XXI

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the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

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ANIMAL EXPERIMENTATION IN RELATION TO EPIDEMIC CEREBROSPINAL MENINGITIS

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Epidemic meningitis, or, as the disease is often termed, cerebrospinal meningitis, is caused by a peculiar micro-organism, *Diplococcus intracellularis* or meningococcus, that gains entrance to the membranes surrounding the brain and spinal cord, where it sets up an inflammation that terminates in death, or, when life is spared, in many instances, in paralysis, imbecility or some other serious condition. Epidemic meningitis, in the past, had been abhorred alike by the laity and the medical profession. To the one it brought consternation by reason of its apparently mysterious onset as well as its terrible effects; and to the other, distress because of helplessness in dealing with so malignant a disease. Now, happily, the situation is wholly changed. Mystery no longer attends the appearance of the disease, and the discovery of a specific method of treatment has brought the malady within the power of medical control. This revolution has been accomplished through the discovery of the specific micro-organism or germ which causes the disease,¹ the manner in which this germ leaves an infected to enter a healthy body,² where it sets up the disease, and, particularly, by the discovery, through animal experimentation, of a curative product, the so-called antimeningitis serum.³

1. Weichselbaum: *Fortschr. d. Med.*, 1887, v, 622.

2. Goodwin and Scholly: *Jour. Infect. Dis.*, 1906, Supplement No. 2, p. 21. Flügge: *Klin. Jahrb.*, 1906, xv, 353. Flexner: *Jour. Exper. Med.*, 1907, ix, 142.

3. Flexner: *THE JOURNAL A. M. A.*, 1906, xlvi, 560; *Jour. Exper. Med.*, 1907, ix, 168. Jochmann: *Deutsch. med. Wchnschr.*, 1906, xxxii, 788. Wassermann: *Deutsch. med. Wchnschr.*, 1907, xxxiii, 1585. Schoene: *Die Therapie der Gegenwart*, 1908, xlvi, 52. Flexner and Jobling: *Jour. Exper. Med.*, 1908, x, 141-690. Flexner: *THE JOURNAL A. M. A.*, Oct. 30, 1909, p. 1443; *Internat. Clin.*, 1909, Series 19, iv.

It would be a mistake to suppose that epidemic meningitis prevails only in the form of epidemics, properly speaking. Indeed, we know that the epidemics represent special manifestations of the disease and that an isolated or so-called sporadic form of the same disease constantly prevails in many parts of the world. The disease is kept alive through these isolated cases and the epidemics arise from them, as a result of certain fortuitous circumstances, of which only a part are at present understood.

Within a decade, the epidemics of meningitis have become more frequent than they were for a period of a quarter of a century or longer before. In the past, the epidemics received the name of "spotted fever," from the circumstance that a hemorrhagic eruption of the skin often attends the disease. The discovery of the germ cause of the disease was made less than a quarter of a century ago, and it has been now demonstrated, beyond all doubt, that this germ is responsible for the epidemic as well as for the sporadic cases of the disease. The renewed intensive studies of meningitis, with the aid of animal experimentation and all the laboratory appliances produced by modern bacteriology that have characterized the period of prevalence of this last epidemic, have shown the manner of infection and thus have pointed the way to the application of preventive measures, and have furnished as well the specific and highly effective therapeutic weapon for its cure.

THE PROBLEM OF FINDING A CURE

The present era of experimental bacteriology has been especially distinguished by the discovery of many of the intimate processes concerned with the facts of recovery from and immunity to the infectious diseases. We are now able to define with singular accuracy the factors involved in these processes. They are not identical in respect to all the infectious diseases; but differ according as these diseases are produced chiefly by poisons elaborated by and liberated from the infecting microorganisms, as in diphtheria, or are caused by poisons which are intimately united with the bodies of the infecting microorganisms, as in meningitis. The manner in which diphtheria has been conquered by means of antitoxin is now so well known, and the factors involved have been so often and clearly presented that they need not be rehearsed here. The problem, however, of securing an

efficient antiserum to be used in combating the diseases produced by the second class of bacteria and their poisons is far more difficult and, up to the present time, has been solved only in small part. Nevertheless, and in spite of many baffling circumstances, the only means at this time approachable was in connection with the production of an antidotal serum. It should be mentioned here that the most perfect therapeutic agents which can be produced or even imagined are the antiserums. This follows from the fact that they are strictly specific agents which act only on the parasites, in this case the bacteria or their products, for which they are prepared, and are practically without action on the body cells. No chemical medicaments are specific in the sense in which the antiserums are; but the most perfect chemical agents act both on the parasites to which they are applied, as in malaria, syphilis, etc., and on the body or organic cells. Their use, therefore, is attended either with a certain amount of inconvenience or even danger, while the use of the antisera is attended almost without inconvenience or danger.

In the production and application of the antiserums we are imitating Nature's method of destroying bacteria within the infected body that she always uses in overcoming the infectious diseases, which pass to favorable termination. Until the introduction of specific serum treatment, it is doubtful whether any of the therapeutic agents employed in their treatment affected, in any essential way, the course of the bacterial diseases. Indeed, what has characterized the bacterial infectious diseases, up to the present time, has been their self-limitation so-called. This self-limitation is determined by the development, in the body of the infected human being or animal, of the very antidotal substances which, in our antiserums, we are endeavoring to procure through animal experimentation. Once having been procured, they can be used to bring about an artificial and premature termination of an infectious disease, since their introduction into the body anticipates their natural formation there, and, in many cases, supplies them under conditions in which their natural formation would be inadequate or fail entirely to take place. The transformation which has been effected in the character and fatality of diphtheria depends on the substitution of ready-made antidotal substances of the nature of antitoxin that,

ordinarily, the infected body must endeavor to produce. Fortunately, the success achieved in the antitoxin treatment of diphtheria has now been repeated in the serum treatment of epidemic meningitis.

HOW THE PROBLEM OF FINDING A CURE FOR EPIDEMIC MENINGITIS WAS SOLVED

It cannot be regarded as remarkable, in view of the appalling mortality and the severe consequences of the disease, and of the absence of all really efficient means of combating it, that an effort should have been made to influence its course by means of an antiserum. At the present state of our knowledge concerning the immunization of animals with bacteria, it could be predicted that the employment of cultures of *Diplococcus intracellularis* for immunization purposes would lead to the development of an antiserum of some degree of potency, but whether this antiserum would prove of any value in the treatment of epidemic meningitis in human beings obviously could not be foreseen.

In carrying into practice the idea of the employment of an antiserum, two methods of proceeding were available. The antiserum could be produced and then applied empirically in the treatment of the disease, or an experimental basis might first be sought, on which the employment of the antiserum in man might ultimately come to be based. The first, or empirical method, as a matter of fact, was followed to a large extent in Germany,² while the second, or experimental method, was employed in the United States.³ How important this difference came to be is indicated by the fact that the early results of the serum treatment of epidemic meningitis as reported from Germany, where the serum was employed chiefly by subcutaneous injection, were so unsatisfactory and unpromising that it is not likely that the serum would have come to be generally employed with confidence;² while, on the other hand, the experimental establishment of the value of the antiserum in controlling experimental meningitis produced in monkeys, when the serum was injected directly into the membranes surrounding the brain and spinal cord, as was done in America by Flexner,³ supplied the actual basis on which the successful serum treatment of epidemic meningitis in man has come to rest.

It is desirable here to recall that the injection of living cultures of *Diplococcus intracellularis* into the serous cavities of small animals, such as mice, guinea-pigs, and rabbits, leads to an intoxication and rarely to an infection causing their death.⁴ The experimental effects thus produced are highly dissimilar to the lesions present in the natural disease in man. As a consequence, the mere combating of this experimental disease by means of an antiserum could not afford an adequate support for the employment of the antiserum in man. Early in his experiments, Dr. Flexner found it possible to produce in certain species of lower monkeys, among which *Macacus rhesus* was shown to be well adapted, an acute inflammation of the meninges, or meningitis, by the direct injection of active cultures into the subdural space of the spinal cord, after which there develop the lesions and sometimes the symptoms corresponding to those present in the natural disease in man (Flexner⁴). This being true, it is a fair assumption that if the antiserum is capable of controlling such an infection, its favorable action in the natural disease in man might be fairly predicted. This fact became an important basis for the employment of the antimeningitis serum in the natural infection with *Diplococcus intracellularis*, constituting epidemic meningitis in human beings.

In working out the properties of the antimeningitis serum, experimentally produced, the important fact was discovered that the serum possesses both direct and indirect power of destroying the meningococci. In common with normal serum, but in a far greater degree, it exercises direct bactericidal effect on cultures of the meningococcus. This influence depends in considerable part on the degree of concentration in which the serum meets the bacteria. Weak dilutions of the serum exercise little or no effect, while strong concentrations have a marked injurious action. Now, this necessary degree of concentration of the serum at the site of multiplication of the diplococci can fortunately be secured by injecting the curative agent directly into the membranes about the spinal cord and brain through so-called lumbar puncture, in which a needle is introduced directly into the spinal canal. The serum thus introduced needs to be applied to the site of the inflammation in a state of strong concentration. If the serum be injected beneath

the skin or into the blood with a view of having it carried to the site of the disease, it suffers, first, an enormous dilution, and, secondly, fails to reach the site of inflammation in any considerable amount, for the reason that substances contained within the blood are eliminated very imperfectly into the cerebrospinal fluid.⁵ As already pointed out, the mistake made by the German school followed on a lack of clear understanding of the essential principles underlying the action of the anti-serum, which they failed to perceive because their employment of the serum was empirical, while, in America, the employment was based directly on the facts brought out by animal experimentation.

There is another point which should not be overlooked in considering the problem with which experimenters were confronted in the production of a curative anti-meningitis serum. Once it was established not only that such a serum could be produced in animals, but also that it was capable of modifying favorably the course of experimental meningitis in monkeys, it became imperative to ascertain whether the serum injected into the membranes of the central nervous system exercised any injurious action on the adjacent sensitive nerve structures themselves. It would have been a hazardous undertaking to have begun the injection by lumbar puncture of the antiserum into human beings, had it not been proved that repeated injections carried out in animals were without injurious effect. This fact was established by the successful treatment of experimental meningitis in the monkey by means of the antiserum, for the injections into the membranes arrested the inflammatory processes and destroyed the diplococci, so that the animals quickly returned to a normal condition, while no perceptible injurious effect resulted from the serum itself.

At this point, a strictly experimental basis had been secured for the employment in human beings of an anti-serum in the treatment of epidemic meningitis. There remained to be determined, however, whether this anti-serum was capable of being produced on a sufficiently large scale to make it available for the treatment of human beings during the prevalence of epidemics of the disease. The earlier experimental work was carried on

5. Flexner and Jobling: Jour. Exper. Med., 1908, x; 141; idem, p. 690.

with small animals, but it became necessary now to turn to larger animals for the purpose of producing adequate supplies of the serum. The horse was the animal chosen, for the reason that its serum is in itself practically innocuous when injected into human beings, and because it yields a large amount of blood readily. It was quickly ascertained that the horse was subject to immunization with cultures of *Diplococcus intracellularis* and would, through successive inoculations and after a time, yield an antiserum of high potency. The method of preparation of the antiserum consists in the injection alternately of cultures of *Diplococcus intracellularis* and an extract soluble in water prepared from the cultures. The animals are, at the beginning of the treatment, highly susceptible to the effects of the injection of the diplococcus, so that it has been found well to employ, first, cultures which have been killed by heat at 60 C., and, later, when the animal has adapted itself to the injections and developed resistance, to resort to the living bacteria. In order to secure a serum rich in the curative or the so-called immunity principles, it was found advisable to continue the process of immunization from four to six months before collecting serum for therapeutic use. The precise period at which the collection of the serum can be begun will depend on the rapidity with which the immunity principles are developed. This is determined by the test known as the standardization of the serum.⁶

The antimeningitis serum, being of the general nature of an antiendotoxic serum, is not subject to standardization according to the methods in use for the antitoxic serums, among which are diphtheria and tetanus antitoxin. While the antimeningitis serum possesses a certain power of neutralization of toxins, or a certain degree of antitoxic strength, this strength is not a correct measure of its therapeutic value, since it does not take account of other and more important immunity principles contained within the serum. Among these latter immunity principles is one of high importance, namely, the opsonins, or bacteriotropins so-called, the action of which is to prepare the diplococci for inclusion within leukocytes, where they are readily destroyed. These opsonins are also capable of being used as a measure of the therapeutic activity of the serum, although the whole

6. Neufeld: Med. Klin., 1908, ii, 1341. Jöbling: Jour. Exper. Med., 1909, xi, 614.

virtue is not supposed to reside in them. At present, the standard of value of the serum is determined by the amount of opsonins present.

If we undertake to summarize the manner of action of the antimeningitis serum in combating epidemic meningitis, we may say (a) that it possesses the power of acting directly on, and inhibiting the growth of, or of destroying outright, the meningococcus; (b) that it possesses the property of increasing phagocytosis and promoting intracellular digestion of the diplococcus, through which the latter is at the same time detoxicated; and (c) that it exerts a certain neutralizing action on the soluble toxic products set free by the growth and by the disintegration of the meningococci (Flexner³).

THE TREATMENT OF EPIDEMIC MENINGITIS IN HUMAN BEINGS WITH THE SERUM

The antiserum had now been perfected. It had also been employed to cure experimental meningitis in monkeys. It had proved to be free of injurious effects when injected directly into the spinal canal of these animals. The question that now pressed was, Would it succeed in curing epidemic meningitis in human beings, and could it be injected with safety into the spinal canal of man?

The first opportunity to test the antimeningitis serum in human beings in the United States occurred in April, 1907. The publication of the effects of the serum in controlling experimental meningitis in monkeys led Dr. Crile,⁶ of Cleveland, to bring to the attention of Dr. Flexner the fact of the prevalence of an epidemic of meningitis in the village of Castalia, Ohio. This epidemic, which was followed later by other epidemics of the disease elsewhere in Ohio, supplied the first opportunity to test the serum on human beings. The serum was first entrusted to Dr. L. W. Ladd,⁷ of Cleveland, who proceeded to Castalia and made the first injections of the serum. Since the experiment now to be performed was of such significance, it assumed a dramatic character. To give some indication of the circumstances under which the serum was first applied in human beings, it should be stated that the village of Castalia has a population of about 600 persons, and that there developed there and in the country adjacent eighteen

7. Ladd: THE JOURNAL A. M. A., 1908, li, 1315.

recognized cases of epidemic meningitis between January and April, 1907. Eleven of the eighteen cases were in adults and seven in children. Among the eighteen cases, there were twelve deaths and six recoveries. Among the latter, there were three recoveries without serum treatment. In all, three cases only were injected with the serum and all recovered. The serum was brought to Castalia in the early part of April at about the time that the epidemic was abating and new cases ceasing to arise. No conclusion, beyond the one that the injection of the serum into the spinal canal was itself not a source of danger in human beings, could be drawn from this small experience.

Epidemic meningitis appeared at Akron, Ohio, in April, 1907,⁸ and embraced about twenty cases. Of these twenty cases, in nine the serum was not administered, either because they occurred before the antiserum was brought to Akron, or for other reasons. Among these nine cases, there was a single recovery. In contrast to this appalling result is the fact that in eleven cases of the disease, established as such by symptoms and bacteriologic examination, and treated with the antiserum, eight patients recovered and only three died. The epidemic continued to extend in Ohio, and appeared at Cleveland and then at still other points, so that now the serum began to be applied immediately as the disease arose. In each locality, however, certain cases were not subjected to the serum treatment and, therefore, could be compared as controls with the cases which were treated with the serum. On the whole, the results were consistent. Without exception, more patients recovered under the influence of the serum treatment than without it.

The testimony of physicians very early was to the effect that the antiserum not only reduced the mortality, but that it exercised a highly favorable influence on the symptoms, course, manner of termination, and liability to relapse, of the disease. Besides the obvious effects on the clinical course of the disease, the serum also produces a marked and readily demonstrable beneficial influence on the inflammation existing in the membranes of the spinal cord and brain. It has now been shown that very soon after the intraspinal injection of the serum, the meningococci tend to be reduced in number in the inflammatory exudate, to disappear from its fluid parts,

8. Chase and Hunt: Arch. Int. Med., 1908, i. 294.

to be taken up partly or wholly by leukocytes, and to undergo disintegration. One of the striking effects of the serum injections is to so injure the meningococci that their cultivation outside the body is rendered difficult or impossible. Along with the destructive action of the antiserum on the meningococci go certain favorable changes in the inflammatory exudate through which it loses turbidity and tends to become clear. Closely associated with the loss of leukocytes by the cerebrospinal exudate, which attends its return to a limpid condition, is the reduction in the number of the general leukocytes of the blood, which, in favorable cases going on to recovery, fall rapidly and even critically in number (Flexner and Jobling³).

Dr. Flexner and his associate, Dr. Jobling, who gathered the first considerable list of cases treated with the serum, believed that their first publication, which included reports of about one hundred cases, was based on too small a number to justify any final deduction as to the value of the serum. Epidemic meningitis, in the meantime, continued to invade new territory in the United States, and to prevail in various localities abroad, so that additional data were being constantly secured concerning the action of the serum.

I will select a highly interesting and important example, which will serve to bring out the striking effects of the serum. Epidemic meningitis had begun to prevail severely in Ireland in 1907. One of the worst centers of the epidemic was Belfast, where a large number of patients with the disease came under the care of Dr. Robb,⁹ who was the physician in charge of the important fever hospitals. His report on the disease states that in the first eight months of 1907, 255 patients were admitted to the hospital, among whom the mortality was 72 per cent. Within the last three months of this period, 45 patients were admitted, and this group showed a mortality of 82 per cent. In September of that year, the use of the antiserum, which had been obtained from the Rockefeller Institute, was begun. The first report deals with thirty patients treated in hospital with the serum, of whom twenty-two recovered and eight died, giving a mortality of 26 per cent. In the precise corresponding period, thirty-four patients were treated outside of hospital and received no serum, among whom

9. Robb: Brit. Med. Jour., 1908, i, 382; ii, 1341.

the mortality was 85 per cent. The marked reduction in the mortality is not the only effect which Dr. Robb attributes to the serum. He points out that the clinical course of the disease is profoundly modified, and that in the patients treated with the serum, the period of illness is reduced, the long chronic course is practically eliminated, and the serious permanent consequences are greatly diminished. The highly favorable effects of the serum, which Robb emphasizes, constituted by no means a unique experience. The earliest observers in this country, and notably Chase and Hunt and Dunn,¹⁰ dwelt on practically the same points. In the large number of reports which have appeared in print in the meantime a virtual corroboration of these early favorable observations has been presented.

THE EFFECT OF THE SERUM TREATMENT ON MORTALITY STATISTICS

Let us consider the influence of the serum treatment of epidemic cerebrospinal meningitis on the mortality of the disease as indicated by a statistical computation. In order to arrive at statistics which are strictly reliable, it is necessary to take into account only the cases in which the diagnosis has been established beyond peradventure. The establishment of the diagnosis is based partly on the clinical symptoms, but chiefly on the bacteriologic examination of the fluid removed by lumbar puncture from the cerebrospinal canal. Ultimately, the bacteriologic diagnosis is the more important, for the reason that, as we now know, other types of infectious meningitis may arise occasionally in the course of the epidemic disease, and the two are subject to confusion.¹¹ Moreover, when the clinical symptoms are alone utilized as a basis of diagnosis, there is always the possibility of confusing diseases not strictly due to inflammation of the meninges with epidemic meningitis.

In recognition of these possible sources of error, Flexner and Jobling³ collated the reports of the disease from many different sources in America and Europe, basing their figures on cases in which the bacteriologic diagnosis was established. They found that the mortality reached by the disease during the height of the epi-

10. Dunn: THE JOURNAL A. M. A., 1908, li, 15. For method of administration see Boston Med. and Surg. Jour., 1908, clix, 743.

11. Dunn: Am. Jour. Dis. Child., 1911, i, 95.

demics in the United States, Great Britain and Germany, was fairly the same and approximated 75 per cent. It is interesting in this connection to learn that the mortality of the sporadic form of the disease, as it has prevailed for the last few years in the United States, has not been considerably below 75 per cent., and it has sometimes been higher. If we consider the extremes of mortality occurring in non-serum-treated cases of cerebrospinal meningitis, proved to be caused by the meningococcus, we shall find that the figures range from about 68 per cent. to about 91 per cent. In his latest publication, Flexner³ has subjected to analysis 712 cases of bacteriologically proved epidemic meningitis, in which the serum had been employed. This series of cases included all ages and periods of life, from infants a few weeks old to adults of advanced years. The collection has been made from a wide area, including the United States, Canada, Great Britain and France, so that it covers a wide variety of cases of the disease treated by practitioners generally, some of whom had had no previous experience with the use of the serum, and others who had used it in several scores of cases. Moreover, the serum had been applied at all stages in the course of the disease, namely, very early and very late after the appearance of the symptoms, and even toward the end of chronic cases. Consequently, in considering the value of the serum, it is desirable to take into account not only the gross mortality, but also the mortality as calculated according to the ages of the patients and the period of the disease at its first application. Epidemic meningitis is not equally fatal at all periods of life. Thus, in the very young the mortality tends to be very high, and in infants approximates 90 per cent. to 100 per cent. The disease is less fatal in older children and in young adults.

The 712 cases, the subject of statistical analysis, had the one fact in common, namely, that the patients were treated with the antiserum prepared at the Rockefeller Institute. As I shall point out a little later, the anti-meningitis serum has been prepared elsewhere, very early in Germany, and later in France. We shall have to consider to what extent the results obtained with the serum prepared at the Rockefeller Institute in New York have been confirmed by the use of similar serums produced elsewhere.

In the 712 cases analyzed, 488 patients recovered and 224 died, giving a gross mortality of 31.4 per cent. If we consider the important age groups, as they are known to affect the mortality, we shall find that among children from one to two years of age, of whom 104 cases were included in the tabulation, the mortality was 42.3 per cent. This figure represents an obvious great reduction, since, as has been stated, epidemic meningitis among infants of such tender ages has terminated fatally in the past almost invariably. Of the age groups between 2 and 15 years, there were 326 cases included in the tabulation, among which the mortality was 23.4 per cent. After the fifteenth year, the mortality, as represented by the tabulation, rises and exceeds 30 per cent. It would seem, therefore, that the most favorable period for the action of the serum, or for the favorable progress of the disease, is a certain middle period between infancy and adult life; but this immediate deduction is not justified for the reason that other factors must obviously be considered, such as the period of the disease at which the serum treatment was begun and the degree of effectiveness in the use of the serum which experience supplies.

Let us consider what the figures become when we analyze the 712 cases mentioned, according to whether the treatment with the serum was begun early or late in the course of the disease. We may choose, arbitrarily, as periods the first three days, the second three days and, then, any time later than the latter. Analyzed in this way, it found that 180 patients were injected with the serum within the first three days of illness, according to the clinical histories supplied, among whom the mortality was 25.3 per cent. In the second period, which extended from the fourth to the seventh day of the illness, shown by the clinical signs, 179 patients were injected, in whom the gross mortality was 27.8 per cent. Now, 129 patients were injected later than the seventh day of the disease, among whom the mortality rose to 42.1 per cent. These total figures indicate unmistakably that early serum injections are more effective than the later ones, which fact has an important bearing on our conclusions concerning the value of the serum. Moreover, if we should pick out one or two especially striking examples from the tabulation, the results become even more impressive. For example, seventeen children ranging in age from a few weeks to 2 years were injected

with the serum in the first three days of illness, of whom only a single one died and sixteen recovered. This result is altogether extraordinary, when it is considered that in this period of life the usual mortality of the disease approaches 100 per cent. It is not probable that such a favorable result can be generally achieved, but that it could be achieved at all is a fact not without profound significance.

It was mentioned that the tabulation showed that in the age period beyond twenty years the mortality was higher than at the earlier periods. It is desirable to ascertain, therefore, whether adults really are, as would appear to be the case, less resistant to the infection or less subject to the action of the serum than younger individuals. Some light is shed on this question by the examination of the results of the serum treatment among adults, observed by those whose experience with the serum has been great enough to make it probable that they would obtain the maximum advantages which its use affords. The reports of such experienced observers as Ladd, Dunn, Sladen and Fulton¹² in the United States, Robb of Belfast, and Netter¹³ of Paris, go to show that adults are not less subject to the curative action of the serum than are younger persons. Among the 712 cases are records of sixty cases occurring among adults and treated with the serum by these experienced physicians that, for all periods of the disease, show a gross mortality of 30 per cent. The largest single series of patients of this age period was treated by Robb. It embraced twenty-four cases, in which only four patients died, giving a mortality of 17 per cent.

We have now considered the effects of the antiserum on the mortality of epidemic meningitis, as shown by the figures compiled on the basis of the employment of the serum prepared at the Rockefeller Institute. The question should now be asked whether these figures are supported by results obtained with a serum produced elsewhere. We are fortunately in a position to answer this question directly. An antimeningitis serum was early produced in Germany at the Institute for Infectious Diseases by Kolle and Wassermann. It was first

12. For American and foreign bibliography consult Flexner, Internat. Clin., 1909, iv, series 19; also Schepelmann, Wien. klin. Wchnschr., 1911, xxiv, 118.

13. Netter: Bull. de l'Acad. de med., séance du 27, 1909; idem, Assoc. Française de pédiatrie, 1910.

employed by subcutaneous injection, but without favorable action. Then, after Flexner's demonstration, it came to be employed by subdural injection and with results in every way comparable to those reported by American observers.

We may confine our detailed examination to one publication emanating from Germany, namely, that of Levy of Essen.¹⁴ In respect to the general results obtained in Germany, we will presently refer to a table that will exhibit them. Levy's results are based on the treatment of forty-one cases, bacteriologically diagnosed, with the antiserum, among which the mortality was 14.6 per cent. There remained forty-nine cases not treated with the serum, which may be regarded as controls, since they arose at the same period, among which the mortality was 61.4 per cent. The general mortality of the disease in and about Essen, exclusive of the serum-treated patients, calculated for the entire period of the epidemic, approached 70 per cent.

Meningitis became epidemic in France at a later date than in America, Great Britain and Germany; and thus it happened that the first serum to be employed there was prepared at the Rockefeller Institute. Somewhat later, the serum prepared by Dopter¹⁵ at the Pasteur Institute became available and seems to have had wide employment. Dopter has reported the results secured in 196 patients in whom his preparation of serum was administered. The deaths numbered thirty-one, which gives a mortality of 15.86 per cent., a remarkably low figure. Among the thirty-one cases there were 10 patients, who, at the time of first injection, were moribund, surviving the injection only a few hours.

In a later report, Dopter assembled reports of 402 cases of epidemic meningitis treated in France with the antiserum, partly prepared by him and partly obtained from America. The number of deaths was 66 and, hence, the gross mortality was only 16.44 per cent. During the same period, the mortality was 65 per cent. among patients not treated with the serum. The difference is so great that it carries its own meaning, especially when it is stated that the 402 cases include patients of all ages treated at the various stages of the disease.

14. Levy: *Klin. Jahrbuch*, 1907-08, xviii, 317. Hohn: *Idem*, 1908, p. 357.

15. Dopter: *Ann. de l'Inst. Pasteur*, 1910, xxiv, 96.

I wish now to reproduce a tabulation (Table 1) compiled by Flexner,³ which exhibits the prevailing mortality of epidemic meningitis in America, Great Britain, Germany and France, according as the patients were or were not treated with the antimeningitis serum. The table has not been brought up to date, so that it does not include the latest American and Parisian figures. But it still suffices to impress its lesson.

TABLE 1.—REPORTED SERIES OF PATIENTS TREATED WITH THE ANTIMENINGITIS SERUM AND THE MORTALITY AMONG NON-SERUM-TREATED PATIENTS

By Whom Reported.	Number of Serum-Treated Patients.	Per Cent.		
		Per Cent.	of Mortality of Patients Non-Serum Treated.	Mortality.
AMERICA				
Dunn *	40	22.5	70	
Chase and Hunt *	12	25	90	
Sladen *	23	13	64	
Fulton *	22	31	78.4	
Koplik *	15	13.3	60	
Ladd *	31	35.5	?	
Morgan & Wilkinson *	10	30	?	
GREAT BRITAIN				
Robb *	90	30	75	
Ker *	30	43	80	
GERMANY				
Krohne †	59	40.6	66	
Schoene ‡	30	27	53	
Levy †	23	21.7	78	
Többen †	29	34	56	
FRANCE				
Netter *	50	18	83	

I have pointed out that one of the striking facts that speak for the value of the serum treatment is its greater efficiency when it is applied early in the course of the disease. How great the difference in effect is, according as the serum is applied early or late, is shown by the next tabulation (Table 2), which is taken from a recent report of Dopter.¹⁵ He adopts the classification introduced by Flexner and Jobling, and considers the cases as they have come under the serum treatment in the three arbitrary periods discussed in a previous section. It should be remarked that Netter's figures are based on cases treated in Paris with the serum prepared at the Rockefeller Institute, while Dopter's figures are based on cases treated in France with the serum which he prepares at the Pasteur Institute.

* Flexner serum employed.

† Wassermann serum employed.

‡ Jochmann serum employed.

TABLE 2.—MORTALITY IN EPIDEMIC MENINGITIS UNDER SERUM TREATMENT: CASES ANALYZED ACCORDING TO PERIOD OF INJECTION

Period of Injection.	Flexner.	Netter.	Dopter.
First to third day....	14.9%	7.14%	8.20%
Fourth to seventh day:	22.0%	11.1 %	14.4 %
Later than seventh day.	36.4%	23.5 %	24.1 %

The influence of age on the fatality of epidemic meningitis has already been alluded to, so that it becomes important to ascertain to what extent this factor can be eliminated through the specific serum treatment. Undoubtedly, increasing experience with the use of the serum is tending to remove the great differences hitherto observed; and the extent to which the age factor is being set aside is well shown by Table 3, taken also from Dopter's¹⁵ last report. In interpreting this table, account should be taken of the fact that the epidemic of meningitis in France is the latest to have appeared in Europe and set in at a time when increasing experience elsewhere had shown the most effective way of administering the serum. This is probably the reason why Netter's and Dopter's figures are the best yet secured. That the epidemic was of average severity is shown by the mortality in non-serum-treated patients, which approximated 70 per cent.

TABLE 3.—GROSS PERCENTAGE MORTALITY IN EPIDEMIC MENINGITIS UNDER SERUM TREATMENT, CASES ANALYZED ACCORDING TO AGE OF PATIENTS

Age Groups.	Reported by		
	Flexner*	Netter†	Dopter‡
Under one year.....	50.0%	50.0%	48.6%
One to two years	42.1%	0.0%§	20.1%
Two to five years.....	23.5%	16.6%	9.3%
Five to ten years.....	11.4%	12.5%	8.5%
Ten to twenty years.....	23.8%	0.0%¶	10.2%
Above twenty years.....	26.4%	0.0%¶	14.1%

I wish now to present a bit of personal evidence in the form of a chart based on the cases of epidemic cerebrospinal meningitis, in which the patients have been admitted to the Children's Hospital in Boston since the year 1900. The average number of patients treated each year in the hospital is twenty. Up to the year 1907, a variety of modes of treatment were employed without accomplishing any real effect in diminishing the fatality

* Rockefeller Institute serum administered by practitioners generally.

† Rockefeller Institute serum administered by Professor Netter.

‡ Pasteur Institute serum. Manner of administration not stated.

§ Six cases.

¶ Eight cases.

of the disease. When the serum treatment was introduced in 1907, the mortality was at its height, that is, at about 80 per cent. The sudden decrease in mortality attributable to the serum treatment is shown in the sharp drop in the curve and its continuation, with minor fluctuations, at this low level.

ATTENUATION OF THE SYMPTOMS

There is still another way in which the favorable action of the serum is disclosed, namely, in respect to

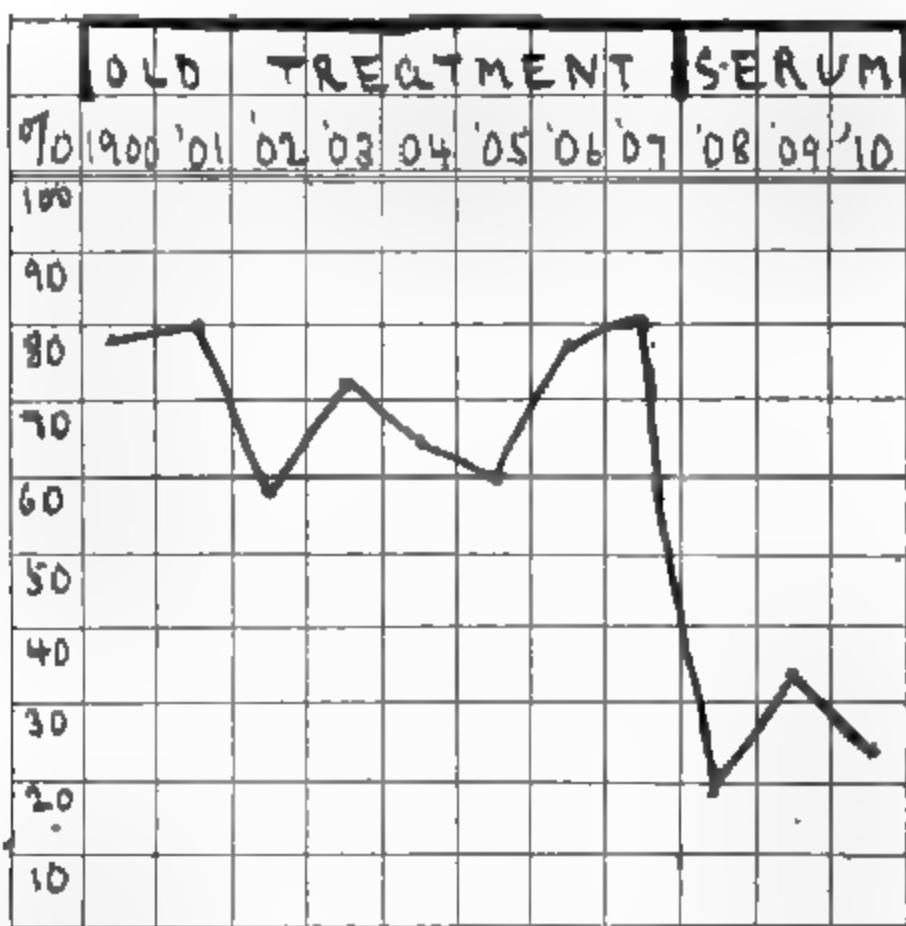


Chart showing the mortality from epidemic cerebrospinal meningitis at the Children's Hospital in Boston before and after the use of the serum treatment, during the eleven years since the diagnosis has been regularly confirmed by bacteriologic examination of the cerebrospinal fluid. The serum treatment was begun after Nov. 1, 1907. Each year shown in the chart is taken as beginning November 1 of the preceding calendar year.

the effects produced on the symptoms, course, duration, manner of termination and permanent consequences of the disease. In discussing this topic, I shall draw largely on my personal experience with more than 100 patients treated with the serum, and I shall also supplement my observations with extracts from the experience of others. I have been able, up to this time, to subject only eighty

of the cases to exact analysis from the present point of view; but I can state that the remaining twenty cases showed the same general effects.

I regard the favorable influence of the serum on the general condition and symptoms of the patients as the most impressive immediate phenomenon. It often happened that within twenty-four hours there was a permanent return to consciousness, disappearance of the mental dulness or delirium, removal of the racking headache, relief of the hyperesthesia and control of the vomiting—all very distressing symptoms that accompany severe infections. To see patients pass within twenty-four hours, after one or two injections of the serum, from a state of great distress and unconsciousness to one of almost normal mentality is something the impressiveness of which is not easily to be overestimated.

Not every patient responds in this rapid manner to the application of the serum. Some patients who recover show a more gradual improvement in condition and symptoms; and still others, and particularly those in the late chronic cases, fail entirely to respond. The effects that are the slowest to yield are rigidity of the neck and Kernig's sign. Children in every other way normal may, at times, be observed playing about the ward while still having the neck retracted and yielding Kernig's sign. In Table 4 I have assembled and analyzed the eighty cases according to the manner of improvement.

TABLE 4.—MANNER OF IMPROVEMENT IN SERUM-TREATED CASES

Immediate and marked.....	34 cases
Immediate and slight.....	14 cases
Immediate and temporary	7 cases
Slow improvement	15 cases
No improvement	10 cases

We find, therefore, that the influence of the serum on the symptoms of epidemic meningitis coincides with the effects exerted on the local inflammatory exudate and the viability of the meningococci. In all but a few resistant cases, the diplococci are quickly rendered incapable of multiplication and the inflammatory process is arrested and brought to rapid resolution.

Another striking effect is on the course of the disease. The average period of duration of cases going on to recovery may be gathered from the calculation of Holt,

based on the New York epidemic of 1905-6. Holt¹⁶ states that in 350 patients who recovered before the serum was perfected, the disease endured one week or less in 3 per cent., and five weeks or longer in 50 per cent. These figures are to be contrasted with those of Flexner and Jobling,³ who found that in 288 serum-treated patients the active symptoms persisted on the averages eleven days after the first injection.

The action on the manner of termination of the disease is also striking. Epidemic meningitis rarely terminates spontaneously by crisis. Indeed, the disease is better characterized as an infection tending to a fatal termination, or to a prolonged course and frequent relapses. Recovery when it occurs tends to be gradual or by lysis and almost never abrupt or by crisis. Yet in 275 serum-treated cases, analyzed by Flexner and Jobling,³ the symptoms were noted to have disappeared by lysis in 200 and by crisis in seventy-three. Hence, it can be concluded that about 25 per cent. of patients recovering under the influence of the serum do so by crisis. Robb, Dunn, Netter, Dopter and others have all observed and dwelt on the amelioration of the symptoms brought about by the serum treatment.

RARITY OF PERMANENT SEQUELÆ

The serious permanent effects of epidemic meningitis are chiefly deafness, blindness, paralysis and idiocy. It is necessary to consider to what degree these blighting results of the disease are affected by the serum treatment. The matter is one of great importance, not only intrinsically, but also because of its bearing on the increased number of persons recovering under the serum treatment who might be permanently injured mentally or physically by the disease. The question resolves itself into this: does the percentage of fixed sequelæ increase proportionately with the percentage of recoveries, or is it larger or smaller?

The evidence, as gathered from the observation of those physicians who have treated many cases with the serum, as well as shown by the published statistics, is to the effect that these sequelæ are rarely encountered in serum-treated patients and, indeed, that there is one sequel only that occurs with any frequency, namely,

deafness. All the other serious effects have been abolished, or nearly so. And in the majority of instances in which deafness has resulted, it has been specifically noted that the condition was already present when the serum was first injected.

Flexner and Jobling³ were the first to point out the infrequency with which serious consequences followed on the epidemic disease when patients were treated with the serum. Since then, and as larger and larger series of cases have come to be reported, other authors have emphasized the same fact, and notably Netter.¹⁷ The serving consequences are of two kinds: one temporary, although persisting for some weeks or months; among these are lesions of the joints and partial deafness. Ultimately they disappear. The others are permanent, and include deafness, blindness, paralysis, etc. The joint affections can themselves be influenced by the serum treatment, since some of them are caused by secondary localizations of the meningococci in the joints, causing suppurative inflammation, which can be terminated, as Ladd⁷ and later Netter¹⁷ have shown, by direct injection of the antimeningitis serum into the inflamed part.

THE ETIOLOGIC DIAGNOSIS OF MENINGITIS

The fact should be emphasized that meningitis is a condition that is produced by several different agencies, nearly all of which are bacteria. Not a little confusion exists, especially in the statistics of meningitis, because in the past it has been impracticable to separate the various etiologic types from one another. With the introduction of the antimeningitis serum, the favorable action of which is limited to one form of the disease, namely, that caused by the meningococcus and designated as epidemic meningitis, it has become necessary to determine with precision this particular infection and to separate it from all the other forms of infectious meningitis. The necessity of employing lumbar puncture for the purpose of injecting the serum into the meninges provided the means of securing, at the same time, the cerebrospinal fluid for bacteriologic diagnosis. Thus, it has come about that more accurate diagnoses have begun to be returned to health officials and that the tuberculous, pneumococcus, streptococcus, staphylococcus

17. Netter : Bull. et mém. Soc. méd. d. hôp. de Paris, 1910, p. 131.

and influenza bacillus infections are being distinguished from true meningococcus epidemic meningitis.

This reform is in its first beginning and is less effective than it otherwise might be, since in many places epidemic meningitis is not a notifiable disease, and the mortality returns of meningitis give no indication of the degree of prevalence of the disease. Even when the death returns are made accurately, they have no value in determining mortality or degree of prevalence of meningitis and the percentage of recoveries, since few or no cases in which the patients recover, are reported at all.

The general mortality statistics on meningitis of the city of New York have been invoked by certain persons holding inimical views regarding the value of the serum treatment of disease generally, to prove that there has been no reduction in mortality of epidemic meningitis as the result of the serum treatment. My personal experience may be cited to illustrate the value, up to this time, of the general health reports on meningitis.¹¹ Outside my regular hospital services, I have been called on to administer the antimeningitis serum in 142 consecutive cases of meningitis which were believed by the attending physicians to be examples of the epidemic disease. On performing lumbar puncture and making bacteriologic examinations, I found that only sixty were cases of epidemic meningitis, while sixty more were cases of tuberculous, twelve of pneumococcus, six of streptococcus and four of influenzal meningitis. Among the sixty cases of epidemic meningitis in which I administered the serum, there were forty-five recoveries, equaling 75 per cent., while of the 82 miscellaneous cases all patients died but one. This experience is by no means unique, but is rather the rule. It is quite certain that all these cases would, under ordinary conditions, have been reported, assuming meningitis to be a generally notifiable disease, as epidemic meningitis; and under these circumstances and in spite of the serum treatment, the records would have shown a mortality of 67.6 per cent. Instead of this the mortality from all the forms together, except the epidemic, should properly have been given at approximately 100 per cent., and of the epidemic disease at 25 per cent.

This is not the only source of error in the health statistics on meningitis. Quite remote diseases are

sometimes mistaken for meningitis. I shall not enter into a discussion of the reasons for the confusion in diagnoses that lumbar puncture is capable quickly of setting aside. During the period mentioned in which I encountered the 142 cases of meningitis, I was called to see eighty-eight other cases that probably would have been reported as examples of meningitis, in which the examination of the cerebrospinal fluid and other tests entirely excluded this condition. Of this series of patients, forty-six recovered and forty-two died. Hence, I have been brought into personal relationship with 230 cases of illness diagnosed correctly or incorrectly as epidemic meningitis, in which cases ninety-two patients recovered and 138 died. All these, it is safe to say, would have been so reported to health officials and would have been recorded as such. Had this been done, a wholly erroneous impression would have been given concerning the mortality in and about Boston of epidemic meningitis, since the introduction into practice of the antimeningitis serum. I am making this elaborate explanation to remove the misapprehension regarding the reliability and value of the statistics as now compiled by our health authorities, so far as they relate to meningitis and its serum treatment. It is obvious that far greater accuracy is now attainable. Whether it is attained or not, it remains to state that the decision as to the value of the antimeningitis serum should be based solely on reports of cases in which the bacteriologic diagnosis has been clearly established.

CONCLUSIONS

The published reports on the action of the antimeningitis serum leave no doubt of its value in the treatment of epidemic meningitis. No one can read the conservative report of Flexner and Jobling,³ who regarded 400 cases as too few on which to base a final decision of the value of the serum, or the reports by many physicians based on observations at the bedside, without being convinced that this severe and pathetic disease has been largely conquered by means of specific serum-therapy. Those who were spared the pain of attending the disease before the days of the serum treatment cannot well imagine how hopeless was the outlook presented to the physician and how helpless he felt in the presence of this malignant malady; and it is, therefore, almost

equally difficult to appreciate, by contrast, what a boon it now is to have at command this powerful remedy. The contrast in the appearance of the wards at the Children's Hospital in Boston now, and as compared with the pre-serum period, is a subject of general remark. Formerly there were almost always to be seen wasted little patients lying with head drawn back, neck rigid, limbs twisted and paralyzed, head swollen by hydrocephalus, and other painful conditions, and remaining thus for weeks or months until death resulted. Now the little meningitis patients are soon laughing, talking and playing with other children, and need not to be kept long in the hospital.

How all this has been accomplished cannot fail to interest all those who are concerned with the conquest of disease. The steps of the achievement I have endeavored to trace in the first part of this paper. The benign result was accomplished by scientific investigations, carried out logically, step by step, and directed toward the definite end of finding a cure for epidemic meningitis. We owe this cure entirely to animal experimentation, for it was through experiments on animals that the additions to our knowledge regarding this difficult problem were won, which culminated in the finding of the curative serum, and thus in the control, to a great extent, of the disease.

It can scarcely be questioned whether this scientific investigation was worth while, or whether the benefit accruing to humanity outweighs the sacrifice of the score of monkeys which contributed to the final result. In estimating the cost of the achievement, the fact should not be lost sight of that while the experimental part of the work leading to the discovery of the anti-meningitis serum need never be repeated, the saving of human misery and of human lives, through the application of the serum, will go on indefinitely until such time as by the rigid application of hygienic preventive measures, many of which still remain to be discovered, epidemic meningitis is eradicated from the world.

The antimeningitis serum was kept under control by the Rockefeller Institute for more than three years while its action was being subjected to the closest clinical scrutiny, during which time it was being supplied gratis to hospitals all over the world. The control has just

been relinquished and its preparation and distribution turned over to health authorities and private individuals. This action has been dictated by the consideration that the value of the serum as a curative agency is no longer under discussion, but has been established by as rigid clinical tests, carried out in many countries, as could well be devised.

We may, therefore, conclude with Dr. Flexner,³ who, in his last report embracing 712 cases of epidemic meningitis, in which the patients were treated with the serum, says:

In view of the various considerations presented, the conclusion may be drawn that the antimeningitis serum, when used by the subdural method of injection, in suitable doses and at proper intervals, is capable of reducing the period of illness; of preventing, in large measure, the chronic lesions and types of the infection; of bringing about complete restoration of health, in all but a very small number of the recovered, thus lessening the serious, deforming and permanent consequences of meningitis; and of greatly diminishing the fatalities due to the disease.

220 Marlboro Street.



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The Rôle of Animal Experimentation in the Discoveries Leading to Our Present Knowledge of the Eti- ology, Prevention and Cure of Diphtheria

W. H. PARK, M.D.

Director of the Research Laboratory, Health Department
NEW YORK

DEFENSE OF RESEARCH PAMPHLET XXII

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
1911

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"NOSTRUMS and QUACKERY"

consists chiefly of reprints of those articles that have appeared in THE JOURNAL of the American Medical Association. While a number of these articles have been previously reprinted in individual pamphlet form, it has been thought desirable to bring all the matter together in one book; "Nostrums and Quackery" is the result.

While this book does not cover so wide a range of subjects as does Mr. Adams' "Great American Fraud" series, yet the concerns dealt with are discussed in greater detail than it was possible, in the nature of the case, for Mr. Adams to do.

While most of the exposes are the result of work done by the American Medical Association, yet advantage has been taken of that done by the Post-office Department through the agency of the fraud order and also by the federal and state officials in enforcing the pure food laws. Some of the subjects are:

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THE RÔLE OF ANIMAL EXPERIMENTATION IN THE DISCOVERIES LEADING TO OUR PRESENT KNOWLEDGE OF THE ETI- OLOGY, PREVENTION AND CURE OF DIPHTHERIA

W. H. PARK, M.D.

Director of the Research Laboratory, Health Department
NEW YORK

The disease which is now called diphtheria is believed to have been prevalent in Europe for a long time. We have reason to think that it occurred at first chiefly in epidemics. The great increase of population and travel during the past one hundred years with its necessary mingling of infected and non-infected persons has aided its dissemination, so that it is endemic in many countries.

THE IDENTITY OF "CROUP" AND LARYNGEAL DIPHTHERIA

It is very important when studying deaths from diphtheria to remember that physicians did not formerly recognize, as we now do, that various forms of ulcerated throat and croup are forms of a single disease. In fact they did not realize this until Bretonneau in 1826 appreciated the fact and gave the disease, however manifested, the name of diphtheria. Bretonneau's statements were soon accepted by many in France, but were not so quickly adopted in the rest of Europe and in America. As late as 1855, he was compelled to reassert his reasons for his conviction, that membranous croup and membranous pharyngitis were both forms of diphtheria, and that either form was capable of communicating the other. He adduced in proof of these statements the details of small epidemics where in the same family, or group of families, different persons presented every form of the disease. He also showed how nurses caring for

cases of "croup" frequently contracted the pharyngeal form of the disease. Bretonneau and those who agreed with him gradually convinced the majority of physicians and so we find such names as inflammation of the throat, sprue, etc., gradually disappearing as they were recognized as forms of diphtheria. The designation "croup" has remained much longer because it designated briefly a form of diphtheria which because of its location in the larynx had special symptoms and required special treatment. This gradual inclusion of all forms of the disease under the name diphtheria has led to confusion among some who do not believe in the value of antitoxin in that they, carelessly failing to note the change in the reporting, have believed that deaths from diphtheria instead of being greatly diminished have remained nearly constant.

The following extracts from the mortality tables of the Department of Health of the City of New York illustrate in an interesting way, how the name diphtheria has supplanted other names for special varieties of the disease.

**GRADUAL SUBSTITUTION IN DEATH CERTIFICATES BY
PHYSICIANS OF NEW YORK CITY OF THE NAME
DIPHTHERIA FOR EARLIER SPECIAL
DESIGNATIONS**

Year	Inflammation of Throat	Sprue	Angina	Croup	Diphtheria
1856	50	49	14	550
1858	70	56	11	478	5*
1860	132	15	37	599	422
1862	68	27	2	685	594
1864	18	4	37	754	781
1865	..	4	5	449	534
1875	758	2,329
1895	342	1,634

* First use of name diphtheria.

As already stated, laryngeal diphtheria has continued to be reported by some as croup, but, as the years have passed, more and more have designated the disease rather than its location, so that the proportion of cases reported as diphtheria has grown ever greater.

Thus in 1860 there were reported in New York City 599 deaths from croup and 422 from diphtheria or an approximate ratio of 1.4 : 1; in 1875 there were reported 758 cases of croup and 2,329 of diphtheria, or a ratio of 0.3 : 1; in 1895 there were reported 342 cases of croup and 1,634 of diphtheria or a ratio of 0.2 : 1.

Exactly the same changes have been taking place in nomenclature everywhere; thus the registrar general's

report for England and Wales, 1898, says, "With regard to the changes which have taken place from time to time in the nomenclature of diphtheria, it is important to bear in mind the following points:

Diphtheria as a distinct affection had scarcely been recognized in England previous to 1855, in which year this disease was first separated from scarlet fever in the national records of the causes of death. As to the unity of diphtheria and croup it states: "The diphtheria epidemic of 1863 was accompanied by parallel movements in the mortality ascribed to croup." After giving more reasons the report continues: "These facts taken in conjunction certainly warrant the assumption that by far the greater number of deaths hitherto attributed to croup have been caused by laryngeal diphtheria."

This gradual recognition of the true nature of croup came about with the clearer understanding of the disease. With our present knowledge we now know that when Francis Home gave the name croup to a certain disease which attacked the larynx and altered the voice, he described by that name true laryngeal diphtheria. Home's accounts of his autopsies make this very clear.

The correctness of the view stated by the registrar general's report, that fatal croup is laryngeal diphtheria, seems so evident that it is difficult to believe that those who affirm they are different diseases, are really sincere.

It would only be necessary for persons having such a belief to look up the cases reported as deaths from diphtheria and they would find that more than 75 per cent. of all such deaths were due to laryngeal diphtheria and that they presented the identical symptoms described by Home in his work published in 1765, entitled "An Enquiry into the Nature, Cause and Cure of Croup." At least, if they believe that croup is not diphtheria, they should eliminate all deaths from diphtheria statistics which are due to croup.

The importance of realizing that the vast majority of cases of croup are diphtheria is, in the first place, that they may be treated as such, and in the second place, that we may rightly judge the benefit derived from anti-toxin treatment as shown in the lessened mortality in cases of croup. It would be as reasonable to assert that cases previously designated meningitis had ceased to exist, because with better knowledge we were able to place them under inflammations due to the tubercle bacillus or to the meningococcus, as to state that croup

seldom occurred because it was now usually reported as laryngeal diphtheria.

THE MEANS BY WHICH WE OBTAINED OUR PRESENT COMPREHENSIVE KNOWLEDGE CONCERNING THE NATURE AND PREVENTION OF DIPHTHERIA

The careful clinical observations of cases and the study of the spread of the disease, without resort to animal experiments, yielded many facts which justified the conclusion that diphtheria was a contagious disease producing definite lesions in the pharynx and larynx. There remained numerous cases, however, the nature of which continued doubtful. There seemed indeed no way to differentiate between these cases, unless possibly a specific microorganism could be discovered. Many attacked the investigation of this problem. Laycock published a paper in Edinburgh in 1859 declaring that diphtheria was due to the *Oidium albicans*. One after another discovered different organisms which they tried to connect with the disease. Klebs demonstrated in 1881, that there were no microorganisms in the internal organs of the majority of diphtheria patients. Two years later he demonstrated that in sections there were near the surface of the membrane, little rod-shaped bacteria. In the same year, Heubner showed that pyogenic cocci were regularly present, but that these, while pathogenic for animals, still did not produce lesions like those of human diphtheria. He came to the conclusion that the organism was yet to be discovered. Koch at that time laid down his three postulates which required as proof that any of the numerous varieties of microorganisms, shown to be present in the throat in cases of diphtheria, was the exciting factor, the finding of the organism in the affected part, its isolation in pure culture and its reproduction of the disease when inoculated in pure culture.

The investigations due to Koch's suggestions led to the discovery of the diphtheria bacillus and of its anti-dote. The following pages will again and again have to record the fact that these results would have been impossible without animal experimentation.

THE DISCOVERY OF DIPHTHERIA BACILLUS BY LOEFFLER

As already stated, the results published prior to the investigations of Loeffler were so inconclusive that many different kinds of bacteria were under consideration as

the possible cause of the disease. Loeffler in 1884 reported the results of a very careful series of studies. He examined sections stained by a special alkaline solution of methylene blue, of the locally affected parts and also of the organs of patients who had died of diphtheria. These investigations showed that the lesions were not always uniform in character, but could be arranged in various groups. The first group was characterized by loss of substance and the presence of greyish-yellow necrotic material, false membranes being absent. All the cases of post-scarlatinal diphtheria belonged to this group. Micrococci, arranged in chains, were found pushing their way in wedge-like masses into the tissues and leaving necrotic areas behind them. Masses of micrococci were also frequently found in the organs of fatal cases. In the second group, thick false membranes occurred on the deeply congested mucous membranes of the throat, larynx or bronchi. Masses of bacteria of various kinds were found covering the surface of the false membranes in disorderly confusion, and more deeply, small rods were found arranged in groups and stained most intensely with methylene blue.

Anatomic and cultural investigations indicated that either streptococci or the bacilli now known to be the diphtheria bacilli were the exciting organisms, but gave no conclusive proofs of the specific significance of either. As other means failed, it was necessary to discover whether either of them was capable of producing in animals a disease analogous to human diphtheria. Experiments were made with pure cultures of the streptococci and other micrococci in a number of animals, mice, guinea-pigs, rabbits and monkeys, partly by feeding, and partly by subcutaneous, intratracheal and intravenous inoculations. Certain animals, especially mice, died from septicemia, with numerous chains of cocci in the blood, but in no case was a disease produced which resembled diphtheria. Since these organisms were only discovered alone in a limited number of cases simulating human diphtheria, and since they have been found similarly arranged in the organs in other infective diseases which are associated with lesions of the mucous membrane, Loeffler came to the conclusion that, in diphtheria also, the chain-forming micrococci were merely of secondary importance, occasionally invading the body under favorable conditions and giving rise to slight or

grave local and general complications. Loeffler also regarded it as possible that the chain-forming micrococci might set up a disease resembling diphtheria by attacking the mucous membranes of the throat and multiplying in the lymph spaces.

With the pure cultures of the suspected bacilli obtained from a number of cases experiments were made on several species of animals. Mice were not affected by inoculations, but guinea-pigs died with characteristic lesions, greyish-white, pseudo-membranous masses at the seat of the inoculation, hemorrhagic edema, effusion into the pleural cavities, lobular consolidation of the lungs and catarrhal inflammation of the kidneys. The bacilli were found usually in small numbers only at the seat of inoculation, but were never observed in the organs. These facts "clearly indicated that a poison produced at the seat of inoculation must have circulated in the blood." Characteristic and striking results were obtained by the inoculation of rabbits. After inoculation of the conjunctiva was performed, the parts became much swollen and covered with whitish tough membranes. Inoculations into the opened trachea produced tracheitis, leading in the majority of cases to the formation of more or less extensive false membranes, which occasionally extended into the bronchi. The operation wounds frequently became covered with fibrinous deposits accompanied by hemorrhagic edema of the neck. Extension of the process from the trachea into the pharynx was never observed. In the false membranes, the bacilli were only found in small numbers and were only observed in those parts of the mucous membrane which were injured during inoculation and which appeared to be totally absent from the internal organs. Since the animals died, in spite of the scarcity of bacilli, Loeffler considered that this confirmed his idea that death was due to the absorption of a chemical poison produced by the bacilli at the site of inoculation.

These results of animal tests established for all time the rôle of the diphtheria bacillus as the sole essential exciting factor in producing diphtheria. The streptococci and other pathogenic bacteria were proved to be an associated and engrafted infection, which at times probably became as dangerous as the diphtheria bacilli, as in the case of a complicating pneumonia or septicemia. The idea of Loeffler that the lesions distant from the

original site of the disease were caused by soluble poisons was proved correct by the work of Roux and Yersin. The injection of the filtrate from cultures produced the same histologic lesions in guinea-pigs as infection with the culture. Without animal tests it would have been impossible to determine this, for the chemical composition of diphtheria toxin is still unknown to us.

The etiologic importance of the bacillus isolated by Loeffler being established, it was possible to establish the nature of doubtful cases. Numerous tests by means of animal inoculations in cases of croup occurring in many parts of Europe and America showed that the opinion of Bretonneau, that fatal croup was almost invariably laryngeal diphtheria, was absolutely correct. Other discoveries were made, such as the fact that there were many mild cases of diphtheria which had not been recognized and had thus been fruitful sources of contagion. It was also disclosed that convalescent cases carried virulent bacilli for weeks or months after recovery and that healthy persons who were brought into contact with diphtheria were occasionally infected and thus might become carriers of diphtheria bacilli, infecting others though escaping themselves.

In all these discoveries it was necessary to use guinea-pigs because it was found that there were harmless bacteria in the throat which so closely resembled the diphtheria bacilli in every respect, except that of poison production, that the two could only be separated and identified through the injection of guinea-pigs.

The information thus obtained proved to be very useful and it was hoped that the intelligent separation, through practical cultures, of suspected cases into those that were diphtheria and those that were not, would make it possible to isolate the one and liberate the other. It was also believed that examination of persons exposed to diphtheria would make it possible to detect the diphtheria bacillus carriers and so prevent their disseminating the germs of the disease. Experience showed that while we could act much more intelligently than before, yet the doubtful cases and the bacillus carriers were so numerous that the problem was too difficult to handle. While the culture test was reliable in cases with exudate, it proved unreliable in convalescent cases and in bacillus carriers because the bacilli might at the moment be so few at the time of making the culture as to be missed,

and the case passed as free from contagion, when, in fact, diphtheria bacilli were present in some recess ready to multiply at any moment. We found that in New York City, during the winter months, nearly 1 per cent. of the children are diphtheria bacillus carriers. These conditions, together with the influence of increasing congestion of the population, brought it about that the deaths from diphtheria (which had diminished for a time after the promulgation of Loeffler's discovery), began again to increase. Fortunately, the discovery by Behring, of the antitoxic power of the blood of animals which have recovered from slight poisoning with the toxin produced by the diphtheria bacillus, gave us a new and potent preventive which also could be used as a cure. This discovery would have been absolutely impossible without animal experimentation, for diphtheria antitoxin is only known by the fact that it acts to neutralize the poisonous action of the toxin. Furthermore, every lot of antitoxin which is sent out must be produced by animals and must be tested in animals.

THE RÔLE OF ANIMAL EXPERIMENTATION IN THE DISCOVERY AND PRACTICAL PRODUCTION OF DIPHTHERIA ANTITOXIN

Behring discovered that not only was an animal, after recovery from a less than fatal dose of diphtheria toxin, immune to an otherwise fatal dose of a diphtheria culture, but also, the far more important point, that the blood-serum contained the protective substance and that this injected into another animal conferred immunity. By testing a number of animals it was found that the horse produced the largest amount of this protective substance. By judicious treatment with repeated inoculations of toxins the antitoxin accumulated in the blood, since it was so slowly eliminated, and the newly formed antitoxin after each injection was added to the major part of that formed in response to the previous injections. It was found that when an animal is injected with the antitoxin produced by one of its own kind, its immunity lasts from four to six months, but when injected with antitoxin produced in another species, immunity lasts only two or three weeks. This difference in the retention of the antitoxin is of both practical and theoretical interest. As human beings always receive antitoxin produced by the horse, the duration of immu-

nity is limited to about two weeks. With each repetition of the injection there is a restoration of the immunity. The duration of immunity as estimated in animal tests has been also proved in man by the exposure of persons during epidemics. The long retention of antitoxin in the bodies of animals of the same species as the one producing it, proves it to be a true cell product.

THE VALUE OF ANTITOXIN IN THE PREVENTION AND TREATMENT OF DIPHTHERIA

I shall first consider the results with which I have been personally familiar. The experience that we have had in New York in the immunization of persons subjected to danger of infection has been very extensive.

The health department inspectors immunized fourteen thousand six hundred persons last year. These were all exposed to contact with diphtheria. In the last three years over thirty-five thousand cases have been treated without a single serious accident. Very few of these contracted diphtheria and not a single one died of the disease. In over 100,000 persons immunized since the introduction of antitoxin there has been but one known fatality due to the serum injection. This child suffered from status lymphaticus and died shortly after an injection of 1,000 units. This was four years ago and followed an injection of serum which had not been refined. The sister of the child received 5,000 units from the same vial and suffered no deleterious after-effects.

Two occasions in which the immunizing value of the antitoxin was strikingly manifested are the following: The first was in an epidemic that was raging in a large institution for children. It broke out in the fall of 1894, a few weeks before we obtained our first antitoxin. Every endeavor was made to isolate not only the sick, but also those from whom diphtheria bacilli were obtained. These measures proved to be insufficient and three or four new cases developed daily. The danger to the children was so great that we decided to use the greater part of a small consignment of antitoxin which we at that time obtained from Germany. All the children were given a moderate injection (300 units). The epidemic ceased at once and no new case developed after the day of the injections for a full ten days when one mild case developed. This summer an epidemic started

in a large insane asylum near New York City. Within six days of the discovery of the first case, many developed. These were not only among patients, but also among the doctors and nurses. As rapidly as possible over two thousand persons were given 1,000 units of antitoxin. No immunized person was attacked and the epidemic was stopped within less than a week. Similar experiences to those we have had in New York City have been met with wherever antitoxin has been used.

TREATMENT

The value of antitoxin in the treatment of disease is not so readily determined as in the prevention. Our experimental tests in animals show that as soon as antitoxin enters the blood-stream it neutralizes any toxin present, but that it only slowly passes through the capillaries to reach any toxin which has passed out previously or is still retained in the mucous membranes at the site of the disease. When antitoxin is subcutaneously injected it is absorbed quickly enough to render the blood-current feebly antitoxic within a few minutes, but strongly so only after several hours, for the antitoxin is apparently chemically allied to the globulins and, like them, is slowly absorbed. Animal tests have demonstrated that by injecting antitoxin into the vein of a patient, we immediately stop further passage of toxin from the blood-stream, and, within a short time, we neutralize any toxin in the tissue fluids and so prevent further injury of cells whether situated at the point of disease or at distant parts. Animal experiments give us no reason to believe that cellular injury already accomplished can be remedied. Antitoxin is really therefore a preventive of further poisoning and cannot restore to health those who have suffered irreparable injury, any more than rescuing from the fire can save one from death who has been burned to an extent incompatible with continued life. Animal experiments give us reason to expect that in cases of diphtheria treated early, the lesions will not advance. In early cases the patients will recover and in the more advanced cases they will improve at least locally, but in many cases they will die from paralysis due to the progress of degeneration from previous injury or complications such as pneumonia due to bacteria, the toxins of which are not neutralized by diphtheria antitoxin.

RESULTS OF ANTITOXIN TREATMENT

It is now sixteen years since the antitoxin treatment of diphtheria began to be used. At first only a small percentage of the patients received the treatment, but steadily year by year a greater proportion of patients were injected with serum until now probably 90 per cent. of all cases are treated with antitoxin. The cases treated in one year in the United States equal at least one hundred thousand and those treated in Europe must total nearly one quarter of a million more. If antitoxin is of real value, we shall find as it becomes more used, a lessened number of deaths, and an increasing consensus of medical opinion in its favor.

THE ABSOLUTE MORTALITIES DURING A LONG SERIES OF
YEARS IN LARGE CITIES AS AN INDEX OF THE VALUE
OF ANTITOXIN TREATMENT

Of all methods at present available, perhaps the least open to error is a comparison of the absolute number of deaths per 100,000 before and after the introduction of antitoxin.

To be of value, statistics of this kind must cover a long period of years. While this, of course, is true for all kinds of statistics it is particularly important in diphtheria in which mortality figures move up and down in irregular waves. These irregularities, however, become apparent only when a considerable number of years are taken into account. For example, in the six years ending 1882, the average of deaths per 100,000 from diphtheria and croup was always above 140 in Baltimore, and reached 200 or over in three of these years. In the seven years following, the mortality fell sharply and continuously until it reached its lowest point in 1889, when it was 52 per 100,000; yet no difference in treatment occurred in 1882.

Care must therefore be taken to secure readings which do not constitute merely a part of an epidemic, unless due allowance be made for this fact. In order to distinguish epidemics, it is necessary to know the average number of deaths for many years. Lack of this knowledge was the weak point in a number of earlier statistic studies and was made use of by the opponents of serum therapy. Further, statistics of this kind ought to be taken mainly from the large cities, for reports of deaths

are usually indifferently kept in the rural districts. It must also be remembered that, at first, antitoxin was used in only a minority of the cases and often at too late a stage of the disease.

In compiling the following statistics, therefore, we have taken only cities having over 125,000 inhabitants, in which the registration of deaths has long been efficient. Apart from these two points the cities were taken at random, some from the United States, some from Great Britain, and the remainder from the continent of Europe. The figures are in all cases from the official records and are, with the exception of Paris, the combined "diphtheria" and "croup" figures. In order to overcome the fluctuations commonly seen in diphtheria mortalities, we have gone back to 1878, i. e., fifteen years prior to the introduction of antitoxin, and have carried our figures up to December 31, 1905, i. e., ten years after the use of antitoxin. We believe that the evidence thus obtained of the great value of diphtheria antitoxin is overwhelming. The figures obtained by us of the deaths in a number of the cities up to the present year show a continuous lessening in the deaths.

Before giving the combined figures of many cities, we shall give those for New York City since 1860 and some for England and Wales and London. The English figures are especially interesting as there has been much discussion of the results in England. The conditions there were somewhat peculiar.¹ The antitoxin treatment was slower in being adopted than in continental Europe and America. Then again, diphtheria had been increasing for a couple of years and this epidemic influence continued until 1899. The fact that during the earlier years membranous croup was not reported as diphtheria and later was included with it, made it possible to mislead by quoting only those reported as diphtheria. This subject has already been fully considered.

STATISTICS FROM NEW YORK CITY

Year	Deaths from Diphtheria and Croup in the Old City of New York	Deaths Per 100,000
1878	1,506	132
1879	1,193	101
1880	2,300	190
1881	3,287	264
1882	2,254	184
1883	1,653	125

1. Thirty-Ninth Annual Report of the Local Government Board for 1909-10, Appendix A, No. 1, pp. 6 and 7.

Year	Deaths from Diphtheria and Croup in the Old City of New York	Deaths per 100,000
1884	1,838	136
1885	2,180	158
1886	2,695	188
1887	3,056	206
1888	2,553	167
1889	2,291	146
1890	1,783	110
1891	1,970	118
1892	2,105	123
1893	2,558	145
1894	2,870*	158*
1895*	1,976*	105*
1896	1,763	91
1897	1,590	81
1898	923	46
1899	1,085	53
1900	1,276	62
1901	1,227	58
1902	1,142	53
1903	1,270	56
1904	1,270	57
1905	860	38
1906	983	39
1907	1,015	40
1908	1,097	41
1909	1,065	39
1910	1,034	37
1911†	787	28

† Estimated for last four months.

* The Antitoxin Laboratory established in the autumn of 1894. Free distribution to the poor begun early in 1895.

The deaths during the first eight months of 1911 are 24 per cent. less than during the same period of 1910. If this improvement continues the death-rate will be 28, or about one-fifth of the average before the introduction of antitoxin. In the whole city of New York, there were reported from January 1 to April 1, 1911, 4,198

DIPHTHERIA IN LONDON

Year	London		Hospitals of Metropolitan's Asylum's Board. Mortality Percentage in Diphtheria Cases Treated in Hospital *
	Rates per 1,000 Persons Living	Notifications Deaths *	
1892	1.96	.44	29.3
1893	3.18	.74	30.4
1894	2.58	.61	29.3
1895**	2.57	.52	22.8
1896	3.07	.59	21.2
1897	2.97	.50	17.7
1898	2.66	.39	15.4
1899	3.05	.43	13.9
1900	2.66	.34	12.3
1901	2.68	.29	11.1
1902	2.31	.25	11.0
1903	1.68	.16	9.7
1909	1.39	.126	9.8

This table is from page 7 of Appendix A of thirty-ninth annual report of the local government board.

* These figures include those dying from "membranous croup."

** Introduction of antitoxin treatment.

cases, and 411 deaths as against 4,957 cases and 597 deaths in 1910. The case fatality was thus only 9.8 per cent. as compared with 12 per cent.

From the last registrar general's report we find that there were in England and Wales 8,609 deaths in 1889, 10,516 deaths in 1894, 10,301 deaths in 1899 and 5,889 deaths in 1908 from diphtheria and membranous croup. The death-rate in 1889 was 30.3; in 1894, 34.7; in 1899, 32.4, and in 1908, 16.6 per 100,000.

Combined statistics of deaths and death-rates from diphtheria and croup in New York, Brooklyn, Boston, Pittsburgh, Baltimore, Philadelphia, Berlin, Cologne, Breslau, Dresden, Hamburg, Königsberg, Munich, Vienna, London, Glasgow, Liverpool, Paris, Frankfurt.

Year	Population	Deaths from Diphtheria and Croup	Deaths Per 100,000
1890	18,526,135	11,059	■■■■
1891	17,689,146	12,389	70.0
1892	18,330,737	14,200	77.5
1893	18,467,970	15,726	80.4
1894	19,033,902	15,125	79.9
1895*	19,143,188	10,857	55.6
1896	19,489,682	9,651	49.5
1897	19,800,629	8,942	45.2
1898	20,037,918	7,170	35.7
1899	20,358,857	7,256	35.8
1900	20,764,614	6,791	32.7
1901	20,874,572	6,104	29.2
1902	21,552,398	5,630	26.1
1903	21,865,299	5,117	23.4
1904	22,532,848	4,917	21.8
1905	22,790,000	4,823	19.0

* Introduction of antitoxin treatment

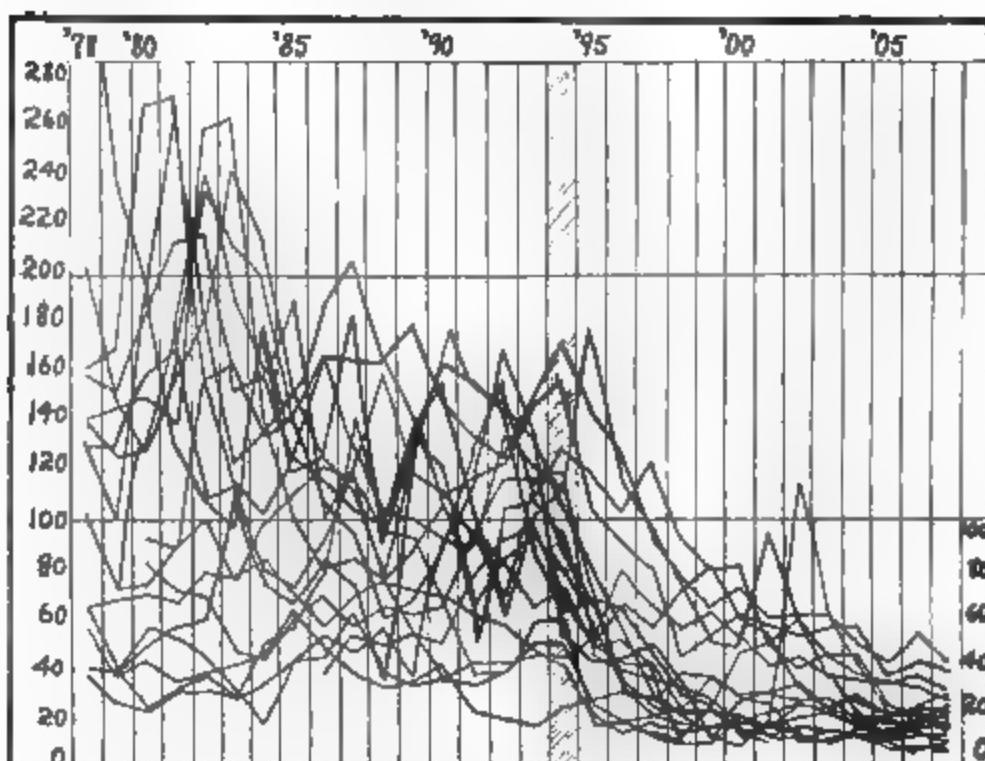


Chart showing deaths from diphtheria (including membranous croup) per 100,000 in nineteen large cities, 1878-1908. The death-rate of each of the nineteen cities is represented by a line. The marked lowering of the death-rates is clear in spite of temporary variations in certain cities.

We see from these figures that although there were marked fluctuations in the absolute mortality per 100,000 in the pre-antitoxin years, in no period did all of the cities show a decrease. Thus in 1884 about half of the cities show a decline and the other half an increase in mortality; the same is true for 1888. Not until we come to the critical year, 1894, do we find almost all the cities showing a like behavior, a drop in the mortality per 100,000. This drop, moreover, has continued until the present time. The difference between 79.9 per cent. in 1894 and 17 per cent. in 1907 is so great and the time of the beginning of the decrease so coincident with the introduction of the antitoxin treatment that it is difficult to attribute any other explanation than that the saving of life was due to antitoxin.

THE RESULTS OBTAINED IN HOSPITALS AND ELSEWHERE IN THE YEARS BEFORE AND AFTER THE INTRODUC- TION OF ANTITOXIN

The figures from the London hospitals have already been given. They show that a mortality of 29 per cent. has been reduced to about 10 per cent.

The Boston City Hospital² has had a similar experience. Before the use of antitoxin about 70 per cent. of the patients presenting intubation cases died; now only about 35 per cent. die.

At the Hospital for Contagious Diseases in New York City very few patients having membranous croup die unless they develop pneumonia. We have little fear of the outcome in any uncomplicated case of diphtheria which receives the antitoxin early.

DEATH-RATE ACCORDING TO DAY OF INJECTION Death-Rate

218 cases treated on first day	4.59
1,153 cases treated on second day	12.50
880 cases treated on third day	16.40
351 cases treated on fifth day	14.24
694 cases treated after fifth day.....	14.15
Total, 3,894 cases.....	10.57

Similar results have been obtained by physicians in Europe and America both in hospitals and private practice. The results are much the best in cases of patients

2. See article by Park and Bolduan, quoting from McCollom's 1905 report.

treated early in the disease. Royer³ has analyzed 3,894 cases of diphtheria in which the patient received antitoxin treatment as to the results according to the day on which treatment was begun.

THE SIMULTANEOUS OBSERVATION OF CASES OF DIPHTHERIA RECEIVING AND NOT RECEIVING THE ANTITOXIN TREATMENT

Fibinger⁴ observed during a period of time a series of cases of alternate patients treated with and without antitoxin.

Among 238 patients treated with antitoxin, 8 died (mortality 3 per cent.).

Among 245 patients treated without antitoxin, 30 died (mortality 12 per cent.).

This method, however, for obvious reasons cannot be extensively used. We made in 1895 a similar test at the Willard Parker Hospital, but the difference in the behavior of the patients appeared to us to be so greatly in favor of those treated with antitoxin that the test after six weeks was stopped and all patients since that time have received antitoxin.

A POSSIBLE DECLINE IN THE VIRULENCE OF THE DISEASE

The observation of the cases of patients who come to us without having had antitoxin treatment, indicate that there has been no marked change in the average virulence of the disease.⁵

THE EXTENT TO WHICH ANTITOXIN IS USED

The observations made under the direction of the Department of Health show that in New York City almost every physician uses antitoxin. There are a good many patients among the poorest classes which do not receive antitoxin early, but this is because a physician has not been called to see the child.

The health authorities of all the northern states have arrangements for making antitoxin available either for the poor or for all classes. So far as I can determine there is no hospital for the care of diphtheria patients in any part of the world in which diphtheria antitoxin is not used.

3. Modern Treatment, Hare, p. 815.

4. Reported by Faber, 1904.

5. See chapter on Mortality in Bacteriology of Diphtheria, Nuttall and Graham Smith, p. 594.

AFTER-EFFECTS OF SERUM INJECTION

Serum carrying the antitoxin is apt to produce after-effects of varying intensity. These effects are due chiefly or altogether to the serum and not to the antitoxin or other antibody which it carries, which is proved by the fact that serum containing no antibodies gives the same symptoms. This fact is of importance, and has led to the elimination of much of the useless serum elements.

FIRST INJECTION

Von Pirquet and Schick have given the name "serum sickness" to the symptoms caused by an injection of serum. After an incubation period which usually covers from five to twelve days, local redness and itching or swelling surrounded by urticarial wheals develop. This is followed by swelling of the lymph nodes, fever, a rash which may spread over the body, edema and swelling of the joints. These symptoms all develop only in severe cases, various combinations occur, and one or another symptom may be most prominent. In the great majority of cases, the rash is the most prominent symptom and is best likened to an attack of "hives" and is of no more seriousness.

Only about 20 per cent. of those injected with serum develop a rash and in many cases only a local reaction occurs.

In a few cases, the reaction occurs more quickly. An immediate general reaction is very rare. This immediate general reaction may be severe and alarming; in a very few instances it has been fatal.

Not all the cases described as fatalities due to the serum will stand close investigation. Some are clearly due to heart paralysis caused by the diphtheria toxemia, and in some the cause is doubtful. These serious accidents have been mostly in adults and many of the cases were asthmatics. How rarely this occurs is seen from our own experience in New York City, already referred to, where only two fatalities occurred since the introduction of antitoxin. If we refer to the number of deaths from diphtheria in nineteen cities for 1894 and 1904 we find there is a reduction of over 10,000. On this basis, one is safe in estimating that the daily saving of life by antitoxin is greater than the total number of fatalities due to its use during the entire sixteen years since its introduction. Further, the danger from im-

mediate general reactions is fortunately almost *nil* in young children. It is in them that the disease causes the greatest loss of life, and antitoxin must be used most freely.

SECOND INJECTION

Arthus, in 1903 at the instigation of Lichet, investigated the results of repeated injections of horse serum into rabbits. Rosenau and Anderson, Otto and others observed the results in guinea-pigs. They found that serum itself gave no toxic effects on the first injection, but if a certain time was allowed to elapse the succeeding injections were toxic. Von Piquet also found that when a second injection in man gave symptoms, these came on much more quickly, at times immediately, instead of occurring after an incubation period of some days. An interval of about ten days must elapse between two injections for this change in reaction to become evident.

With this interval coming between, the second injection in man is apt to be followed by a local reaction in a few hours and a general reaction within twenty-four hours. In some cases the reaction comes on in a few minutes. These reactions may in some cases be much more violent than reactions following the first injection; in some instances they have been alarming. The most important point, however, is the change in the time of reaction.

THE FREQUENCY OF SERUM REACTIONS

The frequency of serum reactions increases somewhat with the size of the dose; thus Weaver⁶ reports that 11

⁶. Arch. Int. Med., 1909, iii, 485.

per cent. of those receiving less than 10 c.c. of serum showed reactions, while 27 per cent. developed symptoms when between 10 and 20 c.c. were given. The serum of some horses is more apt to cause a rash than that of others; further, some people react more readily than others.

ERADICATION OF AFTER-EFFECTS

The first method that would occur to anyone would be to give as much antitoxin as possible with a minimum of serum. One way to do this is to have very high potency serum so that little need be used. If we could separate the antitoxin from the serum elements this would be the ideal way. A long step in this direction has been taken. The antitoxin is bound up with a portion of the globu-

lins. These are separated from the other constituents, giving a refined and concentrated antitoxin. In this way a large number of units can be given in a small bulk, and naturally less foreign proteid than if the same number of units had been given in the original serum.

This globulin solution containing antitoxin can be injected with much less tendency to produce serum after-effects.

After-effects do still occur, and in rare instances are serious, but compared with the benefits of antitoxin, viz., in the prevention of diphtheria and the saving of thousands of lives yearly, they are very small indeed. There is every possibility that with further experimental work, based on animal tests, the antitoxin will be obtained in a practically pure state, and that even these few untoward effects will be wholly eliminated.

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Animal Experimentation and Its Benefits to Mankind

W. B. CANNON, M.D.

George Higginson Professor of Physiology in Harvard University
BOSTON

DEFENSE OF RESEARCH PAMPHLET XXIII

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Elliot.*

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
1912

PAMPHLETS ON
Medical Fakes and Fakers

Consumption Cure Fakes

The ten different preparations discussed in this pamphlet were originally dealt with in THE JOURNAL of the American Medical Association. The matter has been somewhat elaborated, several illustrations added and the whole reprinted and attractively bound in stiff paper cover. The various fakes dealt with are:

<i>Aicsol (Lloyd)</i> *	<i>Lung Germine</i> *
<i>Nature's Creation</i> *	<i>Yonkermann's "Tuberculo-</i>
<i>J. Lawrence Hill, M.D.</i> *	<i>zyne"</i> *
<i>Hoff's Cure</i>	<i>Wilson's Cure</i>
<i>Sartolin</i>	<i>Oxidaze—Oleozone—Hydro-</i>
<i>International Institute</i> *	<i>rine</i> *

[*This matter also appears in individual pamphlet form, price 4 cents]

Cancer Fakes

The United States government has, within the last two or three years, investigated a number of concerns exploiting so-called cures for cancer. In practically every case these companies have been declared fraudulent and the use of the United States mails denied them. This pamphlet contains the exposés of the following concerns:

<i>Rupert Wells</i> *	<i>Dr. and Mrs. Chamlee & Co.</i> *
<i>G. M. Curry</i> *	<i>B. F. Bye</i>
<i>Drs. Mixer</i> *	<i>W. O. Bye</i> } *
<i>Toxo-Absorbent Company</i> *	<i>L. T. Leach</i>

[*This matter also appears in individual pamphlet form, price 4 cents]

Medical Institutes

Some of the cruelest frauds perpetrated by quacks are those carried on under the name of Medical Institutes. This pamphlet deals with three frauds of this kind—

<i>Wisconsin Medical Institute</i>	<i>Epileptic Institute</i>
<i>Boston and Bellevue Institute</i>	

Convictions Under the Food and Drugs Act

The convictions that the government has obtained against the adulterators of drugs and similar preparations are described technically in official documents known as "Notices of Judgment." One hundred and forty-eight of these cases are here abstracted in popular form.

(CONTINUED ON INSIDE BACK COVER PAGE)

Prices of these four pamphlets assorted as desired: One copy, 6 cents; five copies, 25 cents; ten copies, 40 cents; twenty-five copies, 75 cents.

Stamps acceptable for amounts under fifty cents.

ANIMAL EXPERIMENTATION AND ITS BENEFITS TO MANKIND *

W. B. CANNON, M.D.

George Higginson Professor of Physiology in Harvard University

BOSTON

OBSERVATION AND EXPERIMENTATION

Two ways are open to us for obtaining a knowledge of Nature: We may merely watch natural events as they occur, or we may arrange conditions so that the events will appear or disappear, or be modified, as we may wish. For example, the growth of wheat we may study carefully in different native surroundings, or we may place the wheat where we can at will examine the effect on it of heat and cold, sunlight and darkness, wind, gravity, drought and the chemicals of the soil, as these various agencies affect its growth and productiveness. The former method is purely observational, the latter is experimental. The experimental method, in which the conditions to be observed are under control, is, in the main, the distinguishing procedure of modern science.

There is nothing mysterious about experimentation. The method implies first that study of natural events suggests certain explanations for their occurrence, as, for example, that lime in the soil or high temperature makes hard wheat, and that the cautious person, instead of immediately accepting suggested explanations as true, prefers to put them to test.

Of the two methods of learning about Nature, the experimental has proved much more fruitful than the purely observational, chiefly, I think, because experimen-

* In this paper is summarized evidence which has been presented in detail in pamphlets published by the Bureau for the Protection of Medical Research of the Council on Health and Public Instruction of the American Medical Association. These pamphlets, written by experts in the several fields, are referred to in the present paper and should be consulted by persons desiring further information. A price-list will be sent on application to the American Medical Association.

tation is concerned with means of controlling natural forces. The different sciences, however, are subject to the application of the experimental method in different degrees. Most subject to it are chemistry and physics, since of all the natural sciences they are most simple. As a result of the employment of experimentation, astounding advances have been made during the past hundred years in chemistry and physics, and in their industrial applications. All about us are innumerable instances of the practical benefits that have flowed from the experimental study of Nature in its physical and chemical aspects. I need mention only the telephone, the telegraph and wireless telegraphy, steam and gas and electric engines, to indicate how prodigious have been the transformations in civilized society wrought by practical utilization of the scientific discoveries.

There are other sciences, however, that do not lend themselves so readily to investigation by experiment. In consequence our understanding of them is still very defective. Some phases of geology, for example, fall into this class. It has been pointed out that we to-day know little more about the mechanism of the volcano than Pliny when he watched the eruption of Vesuvius that destroyed Pompeii. We cannot control the conditions of volcanic action experimentally, and therefore have only the simple observational method to apply.

THE EXPERIMENTAL STUDY OF DISEASE

In medicine, also, the growth of our knowledge was similarly limited, until about the middle of the last century. Up to that time disease had been studied mainly by observation of sick people. To account for sickness all sorts of theories were advanced, such as bad air, the influence of stars, and mysterious humors and miasms; but these theories were subjected to almost no experimental test. Of course, the highly complex character of living creatures made the beginnings of experimental medicine difficult, for not only do living beings exist together in very complicated biologic relations, but each one is an extremely complex structure, with obscure processes going on within it. In spite of these difficulties, however, the experimental method began about 1850 to be applied systematically to the study of disease, and during the sixty-odd years since then all manner of medical and surgical problems have been experimentally

investigated. What has been the result? According to Osler, the experimental study of physiology and pathology during the second half of the last century did more to emancipate medicine from the routine and thraldom of tradition than all the work of all the physicians from the days of Hippocrates (460 B. C.) to Jenner (1749-1823).

In that marvelous period of transformation of medical knowledge and practice the most fundamental discovery was that of the relation between microorganisms and disease. Pasteur, whose name will be forever linked with this discovery, was a chemist who became interested in conditions which produce bad taste in wines. In the "diseased" wines, as they were called, he found unusual microorganisms. "Did they occasion the bad taste?" he asked. To test this idea, it was only necessary to introduce some of these minute plant growths or germs into good wines. This he did, whereupon these wines also were rendered distasteful, and thus Pasteur's idea was substantiated. Later, when his attention was called to a disease in silkworms, he again found microorganisms present and thought that here, also, they might be the source of the trouble. Applying, as before, the test of experiment, he introduced the microorganisms into healthy silkworms and succeeded in reproducing in them the same disturbance. In this case the disease was no less certainly the product of the germ than the oak is the product of the acorn. The idea that all infectious diseases result from these microscopic invaders was a natural and logical next step. Thus originated the bacterial theory of infection.

This theory was soon tested experimentally by many investigators, who studied not only afflictions of the lower animals, but also those of man. And by the numerous proofs that were accumulated, the theory became so firmly established that we now no longer speak of the bacterial "theory" but of the bacterial or parasitic origin of infectious diseases.

TUBERCULOSIS

The study of diseases which we recognize in human beings is of special interest. First in importance among these, perhaps, is tuberculosis. Klencke (1843) and Villemin (1865) had shown that "tubercle" was infectious by injecting into rabbits tuberculous tissue and

sputum and thus inducing the disease, but its real nature was not clear until Koch, in 1882, announced the discovery of the germ always found with the disease, the tubercle bacillus. The proof that this germ is the cause of tuberculosis Koch obtained entirely by carefully controlled experiments on animals. He separated the bacteria from tuberculous tissues, made the bacteria grow "pure" outside the body, injected these pure cultures into healthy animals, thereby causing tuberculosis, and then recovered from their diseased tissues bacteria in all respects like the original. Conclusive proof was thus given that tuberculosis results from growth of the tubercle bacillus. All the preventive measures in our great modern campaign against the White Plague are the outcome of these and other experiments on animals. The signs in the street cars warning against spitting are there because animal tests proved that tuberculous sputum is infectious.

Twenty-six years ago Trudeau observed that rabbits inoculated with tuberculosis recovered if kept in the open air and supplied with abundant food, whereas other rabbits similarly inoculated and placed in unfavorable conditions of light, air and food succumbed to the disease. By these observations belief in the value of dietetic and open-air treatment was confirmed; and the further demonstration of the efficacy of such care of human beings afflicted with tuberculosis has led to its universal adoption.

What have been the results of these researches on animals? From them we have learned that tuberculosis is not inherited, that it is communicable and therefore preventable, and that in its earlier stages it is curable. In most countries the death-rate from pulmonary tuberculosis has been steadily declining. In Boston, where for twenty years before 1882 (when the tubercle bacillus was discovered) the death-rate had been about 42 per ten thousand, it fell in the subsequent twenty years to 21 per ten thousand. It has since fallen to less than 18 per ten thousand. That decrease has meant a saving of thousands and thousands of human lives in the city of Boston alone. Throughout the civilized world the reduction of mortality has been incalculably great.

The alternative to these happy results has been clearly stated by Trudeau:

If it were not for the knowledge which science has won by animal experimentation in the field of this disease in the last twenty-five years, we should still be plunged in the apathy of ignorance and despair toward it, and tuberculosis would still be exacting its pitiless toll unheeded and unhindered.¹

BUBONIC PLAGUE

Another disease which has brought torment and great disaster to man is bubonic plague. Any one who has read of visitations of this horrifying pestilence knows how mysteriously and how swiftly death spread among large populations, and with what awful terror it was regarded. Defoe, in his story, founded on authentic historical records, called the "Journal of the Plague Year," in London, tells how the streets became hushed as the infection spread insidiously from parish to parish, how the carts moved about at night receiving the heaped bodies of the dead, and how the bodies were dumped pell-mell and by hundreds into huge pits dug for their burial. Thousands died week after week in the city. In the presence of such tragedy the fright and apprehension of the people caused homes to be abandoned, friends to flee from friends; and when the disease developed, the desperate victims often sought death by suicide or became insane. "People in the rage of the distemper," wrote Defoe, "or in the torment of their swellings, which was indeed intolerable, running out of their own government, raving and distracted and oftentimes laying violent hands upon themselves, throwing themselves out of windows, shooting themselves, mothers murdering their own children in their lunacy." Such was the plague in London in 1665, and such it has been in the great populations of the orient in which it has so often raged.²

The mystery of this frightful scourge was lifted when, in 1894, Yersin and Kitasato discovered the germ, *Bacillus pestis*, which invariably accompanies the disease, and when later Simond and others showed, by experiments on animals, that it was spread among rats by fleas, and could be transferred by these same insects from rats to monkeys. The rat-flea also feeds on man when its natural prey is not available. Thus was established the biologic complex by which plague becomes infectious. The attitude of the entire medical world toward the plague was changed by these discoveries, for they sug-

1. Trudeau: Animal Experimentation and Tuberculosis, Defense of Research Pamphlet II, 1909.

2. In India alone, in the one year 1905, the number of recorded deaths from plague was 1,040,429.

gested a definite program for checking or even abruptly stopping an epidemic.³ In former times, when physicians were baffled, the people in their fear resorted to "fortune-tellers, cunning men and astrologers," or placed their faith in "antipestilential pills" and "royal antidotes." What futile weapons to combat fleas and rats! Now traps are set, rookeries and vermin-breeding hovels are torn down, and victims already infected are isolated, so that they shall not be the cause of further infection. Through such measures, where it has been possible to apply them, seriously threatening epidemics of plague have been promptly stopped, and the terror of Black Death has been largely abolished. To experiments on rats, guinea-pigs and monkeys we are indebted for this deliverance.

DIPHTHERIA

Another disease in which marvelous benefits to human beings have been secured through animal experimentation is diphtheria. The peculiar bacteria of this disease, noted by Klebs in 1883, were separated in pure culture by Loeffler, and were inoculated into guinea-pigs and rabbits. The characteristic whitish, tough membrane formed at the seat of inoculation. Since the bacteria were found not at all scattered through the body, but only where the membrane joined the living tissues, the conclusion was drawn that death of the animals was probably due to a poison or toxin produced by the bacteria and spread through the system by the circulating blood. These experiments on animals established for all time the rôle of the diphtheria bacillus and its toxin in producing diphtheria.

An even more practical discovery in connection with this disease was that of the mechanism of immunity. In 1888, Roux and Yersin found that if bouillon in which diphtheria bacilli have been growing is filtered and injected into guinea-pigs, it is highly poisonous in very small doses. The inference that diphtheria germs kill by producing a soluble poison or toxin was thus confirmed. Two years later, von Behring and Kitasato, by injecting first small, then increasing, doses of the toxin into goats, discovered that the animals became adapted or immune to the poison, and further that the immunity depended on an antidote or antitoxin contained in the blood. And still more important and surprising, they

3. McCoy: The Relation of Animal Experimentation to Our Knowledge of the Plague, Defense of Research Pamphlet XV, 1910.

found that blood taken from an immune animal and injected into normal animals would protect these animals against fatal doses of the toxin, or would even cure animals that had shortly before received the fatal dose. If the toxin was mixed with some of the protective blood or serum outside the body, the poison was completely neutralized; and this mixture of toxin and antitoxin, when injected, had no harmful effect whatever.⁴

It is sometimes said by opponents of animal experimentation that the injection of "diseased blood" of an animal into our bodies is loathsome. This feeling, however, indicates an entire misunderstanding of the natural processes by which our bodies are protected against bacterial poison. Our bodies, when we successfully resist a disease like diphtheria, are protected by the development of antitoxin within us, precisely as the bodies of these laboratory animals were protected against increasing doses of toxin. And when we use antitoxin in treating diphtheria we merely take from the blood of a horse, which has been rendered immune by injected toxin, some of the protective substance which the animal has developed and apply it to increase the protective substance which our own bodies are producing.

What has been the practical outcome of these experimental studies of diphtheria? Dr. Park, of the New York City Board of Health, has shown that in 1893 the death-rate from diphtheria in nineteen large cities of the world was slightly over eighty per hundred thousand population; in 1895, when the antitoxin treatment was introduced, the rate began to drop in almost all the cities; and in 1907 the rate had fallen from the eighty per hundred thousand of 1895 to seventeen per hundred thousand. That this extraordinary change has come gradually is explained by the facts that antitoxin was not at once universally employed, that the value of large doses was not at first recognized, and that the supreme importance of early treatment was not immediately demonstrated. Numerous experiences have shown the marvelous effects of instant injection as soon as the disease appears. In the New York City Hospital for Contagious Diseases among 218 patients treated on the first

4. A large body of knowledge, the science of immunology, has been built on these and other experiments on the resistance of organisms to infection. See Gay: Immunology, a Medical Science Developed Through Animal Experimentation, Defense of Research Pamphlet XVII, 1910.

day there were no deaths.⁵ In the Boston City Hospital there have been during the past sixteen years, among nurses, physicians and attendants in the contagious wards, 431 cases of diphtheria. All these persons have received instant treatment; there has not been a single death. The figures that have been gathered are on so large a scale, and are so striking and so precise, that it is impossible to misunderstand them. They prove definitely that the antitoxin treatment has saved from death scores of thousands of human beings.

Death from diphtheria was formerly one of the most frightful modes of death, for the growing membrane led to literal strangulation. Here is Trousseau's classic description of the disease as it occurred in children. It was written about 1870.

The difficulty of respiration increases in severity. Every hour, or every two or three hours, a suffocative fit comes on. The suffocative attacks follow one another more rapidly, and become more and more violent. From time to time the infant, in a state of excitement which it is impossible to describe, suddenly sits up, seizes the bed-curtains and tears them with convulsive frenzy; he throws himself on the neck of his mother or of those about him, embracing them and trying to clutch whatever he can as a something to hold by. At other times it is against himself that he directs his impotent efforts, grasping violently the front of his neck, as if to tear out from it that which is suffocating him. The puffy, purple face and the haggard, sparkling eyes express the most painful anxiety and the most profound terror; the exhausted child then falls into a sort of stupor, during which respiration is difficult and hissing. The face and lips are pale, and the eyes sunken. At last, after a supreme effort to breathe, the agonies of death begin, and the struggle ends.⁶

With such distressing scenes in hospitals in which diphtheria cases were received, can we wonder that it was difficult to secure nurses who would remain?

The introduction of antitoxin not only reduced the death-rate in the remarkable manner already mentioned, but greatly relieved the distress of the afflicted. The injection of the curative serum soon causes the membrane to roll up, and to be so quickly removed that in most cases the danger of suffocation does not arise. At

5. Park: The Rôle of Animal Experimentation in the Discoveries Leading to Our Present Knowledge of the Etiology, Prevention and Cure of Diphtheria, Defense of Research Pamphlet XXII, 1911.

6. Trousseau: Lectures on Clinical Medicine, transl. by Rose and Bazire, i, 342.

the meeting of the American Pediatric Society in 1896, when the first experiences with the new treatment were being reported, physicians spoke of the "marvelous" effects they had witnessed, and declared that in years of practice they had never known such surprising results as antitoxin had made possible.⁷

EPIDEMIC CEREBROSPINAL MENINGITIS

Cerebrospinal meningitis is another disease which has claimed its victims by the scores in epidemics which from time to time have swept through our communities. Its mysterious onset and its dreadful power to kill and mutilate spread consternation whenever it appeared, for the physician was helpless in its presence. About seventy-five of every 100 cases ended in death, and the twenty-five patients who survived were often left blind, deaf, paralyzed or imbecile.

The germ causing this disease was discovered by Weichselbaum in 1887, but it was not until twenty years later, in 1906 and 1907, that Flexner developed an effective treatment. This consisted in producing in the horse an antiserum, in a manner similar to that used for diphtheria antitoxin. The antimeningitis serum was first carefully tested by injecting it into the spinal canal of monkeys previously infected with cerebrospinal meningitis, with the result that the serum quickly restored the animals to health. About twenty-five monkeys were used in the course of the investigation.

Already in nearly a thousand cases of epidemic cerebrospinal meningitis⁸ the death-rate has been reduced from approximately 75 per cent. to about 25 per cent. among patients treated during the first days of the illness. And even when patients treated late are included, the mortality is only slightly over 30 per cent.

The reduction of mortality, however, is not the only benefit. The curative serum greatly shortens the duration of the disease, and, what is more important, the patient usually recovers without the deafness, blindness and paralysis, and the impairment of mental power, so often the consequence in untreated patients. Dunn has contrasted the appearance of the wards of the Children's

7. Boston Med. and Surg. Jour., 1896, cxxxv, 13.

8. This form of meningitis should not be confused with other forms; health board statistics often do not differentiate the various types.

Hospital, Boston, now as compared with the preserum days. He writes:

Formerly there were almost always to be seen wasted little patients lying with head drawn back, neck rigid, limbs twisted and paralyzed, head swollen by hydrocephalus, and other painful conditions, and remaining thus for weeks or months until death resulted. Now the little meningitis patients are soon laughing, talking, and playing with other children, and need not be kept long in the hospital.⁹

Surely this direct result of animal experimentation that has already been manifested in saving for useful lives a half-thousand human beings is to be counted among America's choicest contributions to the "relief of man's estate."

PUS AND SURGICAL ASEPSIS

One of the earliest interests of investigators engaged in experimental medicine was the study of the nature of pus, and of blood poisoning. Pus had been regarded as so necessary for the healing of wounds that its appearance was watched for, and it was designated "laudable pus." Yet accompanying it were much distress and pain and a very high mortality. In our Civil War blood-poisoning (pyemia) was not infrequent, and had a mortality of over 97 per cent. Fifty-one per cent. of the men who had the knee-joint opened died of infection, and of those who suffered a fracture with rupture of the skin about 66 per cent. died. The abdomen and other body cavities were forbidden fields for surgical interference because death so certainly followed the operation of opening them.

Careful microscopic inspection revealed the presence in pus of numerous bacteria. Might not the bacteria cause the pus? If they were excluded might not wounds heal without becoming purulent? Working on this suggestion and on ideas that Pasteur had expressed, Lister watched the healing of surgical wounds in men, and experimental wounds in lower animals, when access of germs to the wounds was prevented by phenol (carbolic acid) sprays and special dressings. The wounds healed without pus! Later it was found that phenol could be dispensed with, and that soaping and scrubbing the skin, and steam-sterilization of instruments and band-

^{9.} Dunn: Animal Experimentation in Relation to Epidemic Cerebrospinal Meningitis, Defense of Research Pamphlet XXI, 1911.

ages were sufficient precautions against purulent infection; but nevertheless Lister's studies were the beginning of modern aseptic technic. All the astonishing advances in surgery during the past forty years have been made possible through these studies, which were inspired by the results of Pasteur's experiments on animals and in which animal experimentation played a highly important rôle.¹⁰

Not only in the development of surgical asepsis, but also in the development of surgical operations have animals been useful to man. The surgeon knows where to approach the brain because the parts of the brain associated with different bodily activities have been discovered through physiologic experiments on monkeys. The restoration of cut nerves and the proper method of suturing them have been learned through a series of physiologic experiments. Many successful operations in the abdominal cavity have resulted directly from tests previously made on animals. The possibility of excising without danger a large extent of the small intestine—an operation sometimes necessary—was thus first demonstrated. Various means of making an artificial opening between the stomach and intestine, when the natural outlet of the stomach is blocked, were also experimentally devised. Proper methods of joining the ends of the severed bowel were, likewise, first shown on animals. More recently, by animal experimentation, the surgery of the chest has been developed; and now apparatus has been invented which permits operations on the heart, the lungs, and other structures of the chest cavity, without the disturbing and possibly serious collapse of the lungs—formerly a constant danger when the thorax was opened. And still more recently, through operations on animals, the surgery of blood-vessels has been perfected to such a degree that the effects of dangerous hemorrhage may be readily treated by the transfusion of blood from a friend or relative to the person in need. These are merely illustrations of the immense advances in surgery during the past thirty or forty years which have sprung directly from experimental methods applied to surgical problems. The release of mankind from distress, disability and long-lasting pain, which has been the consequence of these advances, is beyond all calculation.

10. Keen: Modern Antiseptic Surgery and the Role of Experiment in Its Discovery and Development, Defense of Research Pamphlet XII, 1910.

CHILD-BED FEVER

Similar to the infection of surgical wounds was child-bed fever. Gordon (1792), Oliver Wendell Holmes (1843) and Semmelweis (1847) had urged that this curse of motherhood was contagious and borne from patient to patient by the attending doctor, but little attention was paid to these claims until Pasteur cultivated the bacteria (*streptococcus*) from puerperal infection, and by experiments on rabbits demonstrated its power to produce blood-poisoning. The enormous mortality in the maternity hospitals before child-bed fever began to be treated as a disease of bacterial origin is not now well remembered. Not infrequently in former times these hospitals were regarded as the very portals of death. In all countries the death-rate ranged between 2 and 7 per cent. and at times rose to 14, 20 and once, in the Maternité in Paris, to the appalling height of 57 per cent.! In the sixty years ending with 1875, 363,624 women had died of puerperal fever in Prussia alone. Puerperal epidemics were said to be to woman what war is to man. "Like war they destroy the most healthy, the bravest and the most useful portion of the population; like war they take subjects in the flower of their age and spread terror and desolation throughout the territory which they devastate." These sentences were written in 1870.

In 1879, at a memorable meeting of the Academy of Medicine in Paris, the writer of the above sentences was explaining death from puerperal fever as due to atmospheric influences, overcrowding, the tainted air of old wards, or the power of mind over body, and had expressed his disdain for bacterial contagion by predicting that he expected to be long dead before the specific bacterium was discovered, when Pasteur arose, seized a piece of chalk, and drew on the blackboard outlines of the *streptococcus*. "There!" he exclaimed. "That is the shape of it!"

By use of asepsis, proved effective in preventing wound infection, the mortality from child-bed fever in hospitals has fallen to the neighborhood of 0.1 per cent.—which means an immeasurable reduction of human misery, and the preservation of numberless lives at a time of supreme importance to family and racial welfare.¹¹

11. Williams: *Obstetrics and Animal Experimentation, Defense of Research Pamphlet XVIII*, 1911.

THE DISCOVERY OF USEFUL DRUGS

Mankind has benefited from animals, not only in learning the bacterial transmission of various diseases and in the improvement of surgical technic, but also in the discovery of useful drugs. Indeed the whole modern science of drug-action is founded on animal experimentation. Consider for a moment what blessings have come from such investigations. All the drugs producing sleep which have been discovered during the past forty years have been discovered by experiments on animals. All the local anesthetics, as cocaine, for example, rendering small surgical operations painless, have been discovered by experiments on animals. The only drug which will give prompt relief from the distress of angina pectoris is amyl nitrite—a drug which was discovered during experimentation on animals. All modern drugs for reducing fever; the cardiac tonic, strophanthus; the diuretics, caffeine and theobromin; the emetic, apomorphin—were all introduced through experiments on animals. These do not by any means exhaust the list of medicaments discovered by the experimental method applied in pharmacology. Nor do they indicate all the uses of the method in that new science. Through tests on animals, some drugs whose worth was known have had their action more precisely defined; digitalis, for instance, is one of these. Others have been proved harmful; and still others have had their activity standardized. One of the most interesting examples of the use of animals to test the efficacy of drugs is that of ergot—a drug employed to stop hemorrhage, particularly the dangerous hemorrhage that sometimes follows childbirth. Ergot can thus be tested on an animal and proved potent before being placed in the hands of a physician, or it can be tested for the first time on a woman who is bleeding to death—the choice has to be made.

SYPHILIS AND SALVARSAN

A most thrilling recent development in the study of drug action is the discovery by Ehrlich that through extensive selection chemicals can be found which affect specifically the invading germs, with little or no injury to the patient. This discovery has been utilized especially in the treatment of one of the most calamitous and ravaging of diseases, syphilis. In 1903, experimentation with this disease was made possible by Metch-

nikoff and Roux, who learned that it could be transmitted to monkeys. Later Schaudinn and Hoffmann found the microorganism of the disease, and soon its presence in inoculated animals was demonstrated. At almost the same time, by means of animal experiments, a biologic test, the "Wassermann reaction," was devised, which, when positive, proves the existence of the disease, even in the absence of other signs or symptoms. The value of this test in cases of doubtful diagnosis, or in latent syphilis, is immeasurable. All this experimentation prepared the way for Ehrlich's triumph. After the manufacture and trial of hundreds of substances, Ehrlich found one, number 606 in the series, now known as salvarsan, which when injected into a syphilitic rabbit caused the microorganisms entirely to disappear, and without injury to the rabbit. Then the drug was tested on dogs, without injury. Then two laboratory assistants volunteered to demonstrate the safety of injecting human beings. Only after this was the drug tried on patients. That was hardly two years ago. Even if the final judgment regarding salvarsan sets limits to the first hopes, nevertheless the astonishing results that have already been achieved prove that Ehrlich's experiments on rabbits have added an agency of greatest importance in treating this ancient scourge of social life.¹²

THE USE OF ANIMALS FOR DIAGNOSIS

Prominent among the services of animal experimentation is that of helping in the diagnosis of disease. The *early* diagnosis of infectious disease is essential both for the treatment of individuals and for the prevention of epidemics. We depend on animal tests for determining many of the most serious, socially dangerous afflictions. In tuberculosis, for example, hope lies in early recognition of the nature of the illness. In the first stages the few tubercle bacilli in the sputum may not be observed under the microscope, yet the same material injected into a guinea-pig will clearly demonstrate their presence.

Cultures of the typhoid bacillus, injected into animals, will induce in the blood of the injected animals power to cause typhoid bacilli, and typhoid bacilli alone, to gather in clumps. Thus the blood of the injected animals

12. Churchman: 'The Value of Animal Experimentation as Illustrated by Recent Advances in the Study of Syphilis,' Defense of Research Pamphlet XX, 1911.

can be used to detect the presence of typhoid bacilli in suspected persons as, for example, the apparently normal bacillus-carriers, who are such a menace to public health.

Cholera-carriers, and persons afflicted with cholera in mild form, can be discovered by the same method. Indeed the protection of a country from invasion by cholera involves measures in which diagnosis by animal tests is a very important procedure. When we consider that in a single epidemic many thousands have died, and that wide-spread disturbances of commerce and industry have resulted, we can understand the essential value of finding and controlling the first cases.

In the diagnosis of plague, and to a more or less degree in the diagnosis of dysentery, Malta fever, anthrax, glanders, actinomycosis and other microparasitic diseases, animal tests often play an essential rôle.¹³

More and more we are depending on prevention rather than cure to reduce mortality. Without the means of early and correct recognition of the infectious diseases which animal tests have largely provided, the sanitarians, who stand as sentinels in our great cities and along our coasts, would be deprived of their weapons of defense and be rendered useless as protectors of the public health.

PHYSIOLOGY

The first of the medical sciences to use experimental methods was physiology—the science of the normal working of organs. The abnormal working of organs in disease is necessarily measured by the normal standard which physiologic investigation has revealed. Take away from physiologic knowledge that which is based on animal experimentation and almost nothing would be left! Probably no system in the body more frequently requires earnest study by the physician than the circulatory system. As Erlanger has shown, with much thoroughness, practically all that we know of the course of events in the heart, the proper interpretation of the cardiac sounds, the factors determining blood-pressure, the nervous control of heart and arteries, the intelligent treatment of cardiovascular disease—all have resulted from studies

13. Rosenau: The Rôle of Animal Experimentation in the Diagnosis of Disease, Defense of Research Pamphlet III, 1909. Also Richardson: Animal Experimentation in the Development of Our Knowledge of Dysentery, Cholera and Typhoid Fever, Defense of Research Pamphlet VIII, 1910.

on animals.¹⁴ What is true of the circulation is true also of digestion. Through the activities of a succession of investigators who experimented on animals, we now know the changes which food undergoes in each portion of the alimentary canal, the nature of the digestive juices, the condition under which they are poured out and, to a large degree, the causes and character of digestive disorders. Similarly we are now securing, through the brilliant researches of Sherrington and others, illuminating insight into some of the intricacies of the nervous system. These and many other notable contributions to physiology which almost daily stir our wonder at the marvelous organization of the body are the direct outcome of experiments on animals. It cannot be too strongly emphasized that almost the entire structure of physiologic knowledge on which the modern physician bases his judgment—knowledge which to the practitioner makes all the difference between understanding and blind bewilderment—has grown from the application of the experimental method.

CRETINISM

Physiology in cooperation with clinical medicine has also contributed directly to the cure of human diseases. The distressing malady known as cretinism is due to absence of the thyroid gland from birth. Formerly cretins spent their lives as imbeciles, stunted in stature and hideous in appearance. The semibestial aspect, blubber-lips, turned-up nose sunken at the root, wide-open mouth, lolling tongue, small eyes with swollen lids half closed, the stolid expression of the face, the muddy, dry skin—all combined to make a monstrous creature. The physiologic experiments of Schiff showed that implantation of the thyroid gland in the body would prevent the changes caused by extirpation. Then it was discovered that feeding the gland or injecting the gland-extract was as good as implantation. And now absence of the thyroid can be compensated for by administering by mouth either thyroids, or tablets which contain the essential substance, derived from lower animals. The transformation that occurs in the cretinous idiots, when treated early, is nothing short of miraculous. As Osler has said:

14. Erlanger: Animal Experimentation in Relation to Practical Knowledge of the Circulation, Defense of Research Pamphlet XIII, 1910.

Not the magic wand of Prospero, or the brave kiss of the daughter of Hippocrates, ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed hitherto to live in hopeless imbecility, unspeakable afflictions to their parents and to their relatives.

ANIMAL DISEASES

I have now presented evidence which proves that our knowledge of the disastrous infections and our consequent ability to control them, both in individuals and in communities, have been derived directly from repeated, carefully-planned experiments. The immense saving of life which has resulted is not confined to human beings, however, but is shared by the lower animals as well. I need only mention tuberculosis, anthrax, glanders, hog-cholera, Texas fever and rabies, to indicate diseases which have in the past caused the destruction of domestic herds in enormous numbers, with vast economic losses. Happily the measures taken to protect the lower animals against infection can be more rigorously enforced than those used to save human life, and the results therefore are all the more striking. By means of preventive measures and by protective inoculations, some diseases of cattle have been entirely abolished in this country, and others have been so promptly and radically dealt with that they have seldom made serious headway.¹⁵

PREVENTIVE MEDICINE

That there is the same possibility of protecting human beings against diphtheria and rabies, against malaria and yellow fever, and against many other infections has long been known.

The oldest of the protective measures is that of vaccination against small-pox. This ravaging pestilence has been reduced, in a most striking manner, in every civilized country in which vaccination has been employed. Furthermore, the reduction of the disease and mortality has corresponded directly to the thoroughness with which the populations have been vaccinated and revaccinated. Germany, for example, has had no epidemic of small-pox since the compulsory vaccination law went into effect thirty-eight years ago, whereas in Persia and Asiatic Russia, where vaccination is neglected, small-pox is still

15. Moore: Animal Experimentation; The Protection It Affords to Animals Themselves and Its Value to the Live-Stock Industry of the Country, Defense of Research Pamphlet VI, 1909.

a death-dealing scourge.¹⁶ The claim that the disappearance of the disease is due to a general betterment of sanitation is not supported by our recent experience in the Philippine Islands. The six provinces near Manila, with a population of about one million people, had a record of over 6,000 deaths from small-pox annually before 1907. In 1907, vaccination was completed in these provinces. Since that year, in the six provinces, not one person who had been successfully vaccinated has died of small-pox and only a few cases have occurred among all classes.¹⁷ Inasmuch as animals are used in securing the virus, these triumphs of preventive measures against the disease must be attributed to operations on animals.

Through the application of antirabic virus, death from hydrophobia—a hideous death—has fallen from between 6 and 14 per cent. of persons bitten by rabid animals to a fraction of 1 per cent.; more than 400 persons were bitten by mad dogs and treated by the virus in Paris in 1910, and there was not a single death. Any one who has read the life of Pasteur knows the dramatic story of his experiments on rabbits and his thrilling success in the very first human patients whom he treated. The conquest of rabies must be regarded as one of the greatest services rendered by animals to their fellow-beings.¹⁸

Another victory in the campaign to reduce illness and mortality has been won in the fight against mosquito-borne infections. Yellow fever and malignant malaria contributed more than any other one cause to the failure of the French to build the Panama Canal. The present remarkable freedom from these diseases at the canal, which is permitting the triumphal completion of that stupendous work, is highest testimony to the efficacy of preventive medicine when well-known methods of control can be thoroughly enforced.¹⁹

Of the volunteer regiments mobilized during the Spanish-American War, 90 per cent. became infected with typhoid within the first eight weeks after mobiliza-

16. Schamberg: Vaccination and Its Relation to Animal Experimentation, Defense of Research Pamphlet I, 1911.

17. Heiser: Public Health Reports, 1911, p. 277.

18. Frothingham: The History, Prevalence and Prevention of Rabies and Its Relation to Animal Experimentation, Defense of Research Pamphlet VII, 1910.

19. Marshall: Animal Experimentation in Relation to Protozoan Tropical Diseases, Defense of Research Pamphlet XI, 1910.

tion. In the entire army nearly 21,000 men were disabled by this disease and more than 1,600 died of it. Last year 12,800 men of the American army were mobilized at San Antonio, Tex., for several months. Only one case of typhoid fever, that of a hospital attendant not yet immunized, appeared in the entire force. That this extraordinary phenomenon was due to protective inoculation against typhoid infection, which each soldier received before going into encampment, is indicated by the prevalence of typhoid in San Antonio during the period. The experience of the British army in India has been similar.

The entire modern process of protective inoculation is a direct outgrowth of artificial immunity previously demonstrated in animals (Richardson¹³). And the sole hope of rendering wide areas of tropical country fit for civilized society rests on the possibility of eradicating native diseases through the well-tested and efficacious methods of preventive medicine.

ANTIVIVISECTIONISTS AND THEIR METHODS

Such, then, are some of the benefits to man and to lower animals of the experimental method applied to medical problems. In spite of these benefits, however, strong hostility to this method of studying disease is felt by certain persons who call themselves "antivivisectionists." These persons have no direct acquaintance with the conditions of experimentation; many of them scorn the evidence that any advantage to man has come from studies on animals; to support their contentions they send broadcast pamphlets in which are printed hostile opinions of medical men who are long since dead, men who had no conception of the merciful procedures of modern experimentation and its life-giving results; or they quote the testimony of spurious experts whose reputations were made in literature, art or theology, and not in the service of healing. However well-meaning there motives may be, their literature for years has been characterized by fraud and trickery and evil insinuation which have been repeatedly pointed out, but with no effect.²⁰ These methods of American antivivisectionists duplicate those of the English. The Royal Commission, which has just reported after five years of study and

20. Cannon: Characteristics of Antivivisection Literature, Defense of Research Pamphlet XIX, 1911.

consideration, has declared of the antivivisectionists, their "harrowing descriptions and illustrations of operations inflicted on animals, which are freely circulated by post, advertisement or otherwise, are in many cases calculated to mislead the public." Both in this country and abroad, therefore, the active antivivisectionists have sought, through garbled statements, false evidence and inaccurate description, to cast such discredit on medical research as to give the impression that pain and premature death cannot be escaped through application of the experimental method.

THE ETHICAL QUESTION

Even when these reactionaries grant somewhat grudgingly that the distress of living creatures has been diminished by animal experimentation, they contend that the method of securing this result was immoral and is therefore unjustifiable. What renders the experimental use of animals immoral is difficult to understand when we consider other uses to which they are put. We force the harnessed horse to work, and in time of crisis, we drive him with lash and spur. We rob the mother cow of her calf, and than appropriate her milk. We permit the dehorning of cattle and their branding with hot irons. We do not object to the most shocking barn-yard operations, performed (without the sniff of an anesthetic) merely to make more palatable the flesh we eat. We slaughter ruthlessly, for sport, myriads of birds and beasts. Myriads more we slaughter for their furs and feathers. We kill for food every year in this country more than 50,000,000 beefs, sheep and hogs, and also 250,000,000 chickens, turkeys, ducks and geese. In nineteen of the largest cities in the United States more than 350,000 dogs and cats are destroyed annually, merely to clear the streets. Vermin and wild animals we subject to death in uncertain traps or end their existence with distressing poisons. If all injury and destruction of animal life is immoral, why select as an object for attack the treatment of the relatively few animals employed in the laboratories with the object of reducing pain and suffering in the world?

Surely the life of lower animals is not so sacred that we cannot utilize it for our own betterment. Society protects itself from harm by holding in quarantine dangerous human beings, or by incarcerating them, or even

by killing them. If attacked by a foreign foe, society does not hesitate to send into battle its young men, chosen for their strength, to suffer grievous wounds and death for the social welfare. Such necessary sacrifices of our fellow men are among the tragedies of social existence. The sacrifices of animals, in various ways so essential to the continuance of the human race, may be regarded as among the tragedies of their existence. But of all these, what sacrifices could be more thoroughly justified morally than those of experimentation, which have contributed so greatly to the reduction of suffering and to prolongation of life, both for men and the animals themselves?²¹

PRECAUTIONS AGAINST PAIN

I do not wish to give the impression that any one engaged in animal experimentation would, under any circumstances, justify the infliction of needless pain. That animals are in fact used humanely for the purposes of medical research has been again and again maintained and demonstrated whenever the question has been carefully examined. The English laboratory inspectors and the English Royal Commission are unanimous in testifying to the absence of cruelty in experimental procedures. In this country practically all institutions in which animals are used for medical and biologic research have adopted, by public and corporate action, regulations which place control of experimentation with the laboratory director. These regulations provide for the bodily comfort and the sanitary surroundings of the animals, and require all operations to be sanctioned by the director, who is held responsible for the importance of the problems studied and the propriety of the laboratory procedures. Furthermore, the regulations require all operations likely to cause greater discomfort than anesthetization itself to be done under anesthesia, and to be followed by painless death. Only the director can make exceptions to these last provisions, and he can do so only in the rare cases in which anesthesia or death of the animal would defeat the object of the experiments.²²

The laboratory director, of all men, is most likely to know what is being done by those about him; more

21. For further discussion, see Angell: The Ethics of Animal Experimentation, Defense of Research Pamphlet V. 1909.

22. Cannon: Medical Control of Vivisection, Defense of Research Pamphlet XVI, 1910.

than any one else he is responsible to his institution, to the public interests and to his professional ideal; and his position is a warrant of his trustworthiness. To the laboratory director, therefore, the medical profession looks for the exercise of that enlightened compassion which lies at the heart of all medical service.

OBJECTIONS TO PROPOSED LEGISLATION

In spite of accumulated evidence that animal experimentation is conducted in a humane manner in this country, and that strict precautions have been taken against infliction of unnecessary pain, every year in one state or another a "mild" restrictive bill is alluringly presented by the antivivisectionists. Its ostensible purpose is, not to prevent "legitimate vivisection" by responsible investigators, but to stop the practice among the unskilled—for example, the medical student in his room. Examination of the bill reveals, however, that no provision is made for spying on the medical student in his room, but that every arrangement is made for inspection of the responsible investigators. To many persons inspection seems reasonable; they approve of going at least so far with the petitioners for legislation. The medical profession, however, has in the main offered objections to the proposed inspection.²³

These objections are based to some extent on the attitude of the antivivisectionists toward inspection as it has been carried on in England during the past thirty-six years. During all this period no noteworthy abuse of animal experimentation has been revealed by the inspectors. The inference drawn by the antivivisectionists is that occasional inspection is futile; indeed, they declare that, unless an inspector is in the laboratories continuously during all operations, horrible abuse of animals is sure to occur.²⁴ The impossibility of providing for such constant oversight would suggest to a person of common sense that a reasonable reliance be placed on the good

23. It is, perhaps, unnecessary at this point to indicate the absurdity of the cry for the "open door." No one of insight and judgment is excluded from laboratories of medical research. In fact, in every laboratory with which I am acquainted the doors are freely open to biologists and persons with medical training. To be sure, not everybody is welcomed, but not everybody is welcomed to a hospital operation. The surgeon, operating in a home does not permit the "open door;" he even goes so far as to exclude close relatives of the patient. Yet he does not become thereby the object of malignant suspicion.

24. Minutes of Evidence, English Parliamentary Commission on Vivisection, 1905-6, Coleridge's testimony, *passim*.

will and natural humanity of those engaged in research. The agitators in this country, however, have argued that when danger of wrong exists, as in the conduct of a bank, for example, inspection is provided, and therefore laboratory inspection should be provided. An important defect in this argument rests in its application. For the inspection of banks experts in banking are appointed, but for the inspection of laboratories experts in experimentation are definitely excluded in the proposed legislation. For this important work the antivivisectionists desire only their own representatives. In the opinion of the experimenters such persons, untrained in observing and judging animal reactions, and lacking any insight whatever into the extraordinary complexities of medical investigation, are thoroughly incompetent. Indeed the most charitable interpretation to be placed on the ridiculously false and misleading statements continually made by these persons is that they are profoundly ignorant of processes which the laboratory workers have spent many years in learning—the most involved and entangled processes in nature, those occurring in highly organized animals.

Apart from objecting to inspection because it has not satisfied the antivivisectionists themselves, because it has not revealed abuses and because incompetent inspectors are insisted on, we may reasonably regard it as merely the first step in an effort to stop experimental medicine absolutely. In Great Britain, where legal restriction has gone farthest, there are no less than fifteen antivivisection societies urging that experiments on animals be abolished. In this country there are at least six such organizations whose aim likewise, expressed or implied, is abolition. The agitation for "mild" bills, for inspection or for slight restriction by these groups of agitators is, under the circumstances, properly regarded as merely the initial move toward total suppression of what has been demonstrated in these last sixty years as the most powerful instrument of medical progress that has been devised.

THE TWO PARTIES

The issue then is joined. On the one side are the antivivisectionists who insist that animals shall not be experimented on, even though mankind may thereby be saved throughout coming centuries from pain and premature death. On the other side are the investigators, successors

of those who first applied to medical problems the experimental method, a method which, besides delivering into our hands the unlimited energies of the physical world, has in a few decades wrought marvelous advances in our ability to conserve human life. These men realize that numerous sources of distress are still unexplained. Measles, scarlet fever, infantile paralysis, fatal diseases of the kidneys and liver, cerebral degenerations, the awful scourge of cancer²⁵—almost all progress in our knowledge of these afflictions has come from experiments on animals—but how much more remains to be accomplished! Men and women and children, whose suffering extends to every one bound to them by the strong ties of love and sympathy, daily go down to death because the disease is a mystery and its cure unknown. Who shall say that experimental medicine shall not continue to bring its blessings? In the eager search for more light, who shall decide the critical case involving pain to animals? The antivivisectionists maintain that they should decide; the physicians, on the contrary, urge that the decision remain in their control. The antivivisectionists, ignorant of the problems and methods of medical research, limit their humanity to the welfare of the laboratory animals. The physicians, perceiving that more power to fight disease can only come from more knowledge, trust the deeper humanity of the investigators who are seeking that knowledge. In the end society, which reaps the benefit of medical progress, must determine which of these contending parties shall prevail.

240 Longwood Avenue.

25. Ewing: Animal Experimentation and Cancer, Defense of Research Pamphlet IV, 1909.

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The Influence of Antivivisection on Character

W. W. KEEN, M.D.
PHILADELPHIA

DEFENSE OF RESEARCH PAMPHLET XXIV

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"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

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The Influence of Antivivisection on Character

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THE INFLUENCE OF ANTIVIVISECTION ON CHARACTER*

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"In this controversy [vivisection] there should be no bitterness. . . . Do not let us attempt to browbeat or call names. . . . Vivisection tends to weaken character. . . . Nothing which hurts the character can be right."—Rev. Dr. Floyd W. Tomkins, President of the American Antivivisection Society, in the *Ladies' Home Journal*, March, 1910.

I accept the test proposed by Dr. Tomkins, and quoted in the above motto, "Nothing which hurts the character can be right." Let us, therefore, study what is the effect of antivivisection on the character of its advocates.

I. VIOLENT PASSIONS AROUSED BY ANTIVIVISECTION AGITATION

The most violent and vindictive passions have been aroused and fostered, especially among women — the very flower of our modern civilization. Let us see whether they have shown "bitterness" or "called names." I have rejected much oral testimony I could use and have drawn my evidence from only a very small portion of the literature at my disposal.

Herewith I reproduce (Fig. 1) the photograph of a remarkable letter which contains an asserted prayer to the Deity calling down curses by "a dozen women" on my long-since sainted mother. It needs no comment from me save that the "horror" mentioned in this letter was excited by an article which I published in the *Ladies' Home Journal* for April, 1910, in which I recited a few of the *benefits to humanity* which had resulted from vivisection. The only clue even to the place from which the letter comes is the postmark.

* An address read before the Surgical Section of the Suffolk District Medical Society, Boston, March 20, 1912. Reprinted by the kind permission of the editor and the publisher from the Boston Medical and Surgical Journal, May 2 and 9, 1912.

Arch-Fiend:

I read with horror you article in the Ladies' Home Journal on vivisection.

I hope your mother if she is living will die in the most terrible torture, and if she is dead that her soul will never know rest for having given life to such a vile monster as you is the nightly prayer of
a dozen women who indicated this

Fig. 1.—Photograph of a letter received by myself in August, 1910. Both envelope and letter were typewritten, with no place, no date and no signature; only the postmark showed that the letter came from Los Angeles.

Let me quote another earlier anonymous letter I have before me. This is from Philadelphia. Instead of the usual address "Dear Sir," it begins, "You Fiend." I had not then been promoted to "Arch-fiend" in Satan's Hierarchy. The writer exclaims, "Oh, that you all could be put through the same torture that you inflict on these helpless ones." As I am not a vivisectionist this ardent wish fails to terrify. I am an advocate of vivisection because I *know* how greatly it has helped me during all my professional life in saving life and lessening suffering.¹

If two letters will not convince, here is a third. This, from Baltimore, also the result of the same article, was from a writer who had the courage to sign her name and address.

"You would appear even the more fiendish on account of your superior intelligence. . . . The future of a vivisectionist is a veritable hell. You, I understand, are a man advanced in years [the calendar, alas! seems to justify this shocking statement] soon to go before the bar of justice. Can you meet your God with the terrible cries ringing in your ears of these creatures, our helpless brothers, made by his hand, that you have drawn and quartered? How they must haunt you. . . . When your time comes to die, every cry of pain and anguish that you have been the cause of producing in these helpless creatures will follow you to the depths

1. In the American Journal of the Medical Sciences for July, 1865, p. 67, Dr. S. Weir Mitchell, the late Dr. Morehouse and I published a paper on the "Antagonism of Atropia and Morphia," based on observations and experiments in the Army Hospital for Injuries and Diseases of the Nervous System. The reason which caused us to make this investigation was that we desired to find better means for "soothing the pain of those terrible cases of neuralgia" following gunshot-wounds of large nerves. These are accurately described in the paper as causing "anguish" and "agony"—no word could be too strong. Accordingly, in our efforts we tried a number of common and some uncommon drugs, and finally found that morphin (the active principle of opium) was the best remedy and yet had many disadvantages. Ultimately we found that by combining with it a certain amount of atropin (the active principle of belladonna) we obtained the best results. The facts discovered in our investigations have long since become merged in the common knowledge of the profession, and standard tablets with different proportions of the two drugs are manufactured and used all over the world. Most of our patients operated on (entirely by hypodermic injections) were sorely in need of relief. A few were convalescents. In all cases we avoided telling them what drug was being used, for every one knows how imagination, fear or other emotion would alter the rate of the pulse or of the breathing. Not one man was injured in the least. Not one ever complained. Many thousands of human beings have been greatly benefited and many lives have been saved through the knowledge thus obtained.

I have expressly mentioned these facts in some detail because we have been attacked in their pamphlets by the antivivisectionists for these experiments, which are described as "human vivisection."

of hell." Yet I have "drawn and quartered" not even so much as a mouse.

But this same lady tells me that she had survived one of the most serious abdominal operations that could be done — a hysterectomy. This operation was so perilous that until Lister had devised the antiseptic method it was never even thought *possible*, and its success at the present day is due chiefly to experiment on animals. The writer of the letter, therefore, is herself a witness to the benefit of vivisection.

Later on she says, "If they would only use vivisectors for their experiments, it would soon be considered unnecessary." Her gentlest wish, therefore, is for human vivisection, and doubtless "without anesthetics." Per contra, in the newspapers of May 6, 1911, a dispatch states that seventeen medical students had offered themselves for experimental inoculation with cancer, an offer which was, of course, refused, as animals can be used.

A curious statement in the letter is, "I understand the Rockefeller Institute has had four or five of its laboratories burned, the animals destroyed, rather than have them fall into the hands of these wretches, and if this thing were more widely known, every medical college in the country would be razed to the ground and the doctors tarred and feathered." The insurance companies, I am quite certain, have never heard of the one laboratory which the Rockefeller Institute possesses having been burned. But what a strange exhibition of kindness it is to gloat over the fact that the poor animals in these supposed laboratories had been roasted to death "without anesthetics."

If three instances are not sufficient, here is a fourth — a signed letter from Chicago. Referring to one case which I had published as an illustration of the value of vivisection in saving human life, she says, "My sympathy for the parents of that young man . . . would have been deep, but not so keen as for a mother dog who saw her puppy tortured to death on a dissecting table. . . . Even if you did save a man's life, *was it worth while?*" (Italics in the letter!) This lady wrongly assumes that the puppy was "tortured to death," i. e., without anesthetics. This, I am glad to say, is not true, as I shall show later on. To her question, "Was it worth while?" I can only say, "Ask his father and mother."

And this is the ennobling influence of antivivisection!

A fifth communication is from a lady who was personally acquainted with myself and my family. She sent me a pamphlet with some good advice, ending with the terse injunction, "Do God's work, not the Devil's," and had the courage to sign her name.

A sixth lady sent me (anonymously) an article from one of our magazines, with many marginal annotations and much underscoring. From this I select a few sentences.

"Millions of people regard him [the vivisector] with loathing, and shudder with horror at his name. . . . Frightful as the sufferings of this tortured dog must be, I would rather be in its place than yours when your soul is summoned to its final judgment to receive judgment without mercy. [This seems to be a favorite threat of my correspondents.] May God so deal with every fiend incarnate who has thus tortured defenseless creatures. . . . All the demons and fiends do not dwell in Hades. Some are made in the image of God, but have hearts blacker and more cruel than the arch-fiend himself. These are the vivisectors who 'benefit' mankind."

I have received very many more such letters — usually anonymous. These six may serve as samples.

I would willingly accept the supposition of unbalanced minds as an explanation and palliation for such letters but for their number and for the fact that they so entirely coincide with almost all the "repulsive literature" (to use Lord Coleridge's words) published by the various antivivisection societies.

A brief search through only a part of my file of this antivivisection literature enables me to cull the following evidences of a similar debasing violence and vindictiveness. The list could easily be extended.

"The art of torture has been carried to a perfection which the devildoms of Spain in the old days of the Inquisition could not equal in ingenuity or pitilessness."

"Vivisection is the anguish, the hell of science. All the cruelty which the human or rather the inhuman heart is capable of inflicting is in this one word. Below it there is no depth. This word lies like a coiled serpent at the bottom of the abyss."

"Animals are dissected alive — usually without the use of anesthetics."

"The vivisector keeps his victim alive while he cuts it up."

"Vivisection founded on cruelty, supported by falsehood, and practiced for selfish ends."

"The vivisector is less valuable to the world than the animals he destroys."

"A thing I know to be damnable whatever the results."

"An organized system of barbarity."

"Vivisector and criminal become interchangeable terms."

"Cowards who perpetrate hideous crimes."

"Experiments on living animals is a system of long-protracted agonies, the very recollection of which is enough to make the soul sick as if with a whiff and an after-taste of a moral sewer."

"Impious barbarity of the vivisector."

"All other forms of sinful cruelty are comparatively trifling compared with the horrors of vivisection."

"Deliberate dabbling in blood and agony."

"Cruelty the inevitable and odious spawn of secret vivisection."

"Blood-stained hands of the grim tormentors."

"Bloody mass of agony."

"Devilish inventions of unbalanced mentality."

At a hearing before a committee of the Legislature of Pennsylvania, I heard myself and others who were advocating the humane work of vivisection called "hyenas" by a woman.

Briefer descriptive terms are as follows:

scientific hells	temples of torment .
torture-house	cruelty of cruelties
orgy of cruelty	infernal work
halls of agony	hellish wrong
inhuman devil	devil's work
devils incarnate	lust of cruelty
scientific murder	scientific assassination
abominable sin	torture of the innocent
devilish science	black art of vivisection
fiends incarnate	satanic
damnably mean	fiends
arch-fiend	human monsters
master demon	demons
diabolical vivisection	

Antivivisection writers nearly always state, assume or imply that all experiments are "tortures," i. e., that anesthetics are not used. This is wholly erroneous.

In Great Britain, where all experiments are returned to the government, the following table for 1906 (the latest I happen to have) will show how utterly indefensible is such an assumption. It is a fair presumption that about the same average exists in the United States.

	Per cent.
Inoculations, etc., not involving any operation.....	93.96
Animals killed under anesthetics.....	3.44
Animals allowed to recover from anesthetic but nothing likely to cause pain and no further operation allowed without anesthetic	2.60
	<hr/>
	100.00

In other words, only *twenty-six animals out of 1,000* could by any possibility have suffered *any* pain, and very few of these any serious pain. Is this the torture and agony so constantly harped on?²

Many of the instances cited in antivivisection literature are taken from researches — such as Magendie's — which were made before anesthetics were discovered, over sixty-five years ago.

The rest in which real cruelty was inflicted, and which if done now would be condemned by all modern research workers as freely as by the antivivisectionists themselves, were done almost wholly on the Continent, and often by persons who are now dead. In discussing vivisection to-day, these should be excluded, or their dates and countries indicated, for the public, ignorant of medical history, is misled into supposing that these persons are living and practicing these methods to-day and in America.

In one of the anonymous replies to my paper on the "Misstatements of Antivivisectionists," I am represented as the apologist and advocate of experiments of which twice over at the Senate Committee hearing and again in my letter to Mr. Brown I had expressed my utter disapproval. I am always willing to face a truthful charge, but it is a hopeless task to meet untruthful charges, especially when the author is ashamed of his own name.

"Hell at Close Range" is the title given by Miss Ellen Snow to a leaflet dealing with the work of the Rockefeller Institute. One would scarcely expect such a fierce heat from so frosty a name.

2. Since this address was delivered the report of the British Royal Commission on Vivisection, on which the antivivisectionists were represented, has appeared. One of their *unanimous* conclusions (page 20) is as follows:

"We desire to state that the harrowing descriptions and illustrations of operations inflicted on animals, which are freely circulated by post, advertisement or otherwise, are in many cases calculated to mislead the public, so far as they suggest that the animals in question were not under an anesthetic. To represent that animals subjected to experiments in this country are wantonly tortured would, in our opinion, be absolutely false."

This clear statement should end this calumny.

At this institute, by experiments on twenty-five monkeys and 100 guinea-pigs, most of which animals recovered, has been discovered a serum that has brought the former death-rate of cerebrospinal meningitis of 75 or 90 per cent. down to 20 per cent. and less. Is it because of this beneficent work that it is called "Hell"?

At this institute has been discovered a means of transfusion of blood that has already saved scores of human lives. Is this the reason for calling it "Hell"?

At this institute a method of criss-crossing arteries and veins, which almost always run alongside of each other, has been discovered by which impending gangrene has been prevented. Does this make it a "Hell"?

At this institute the cause and the cure of infantile paralysis are being sought. Are such investigations carried on in "Hell"?

Miss Snow in this same leaflet expresses in italics her horror at the idea of the proposition of the institute "to build a hospital where the experiments may be continued on human beings." It may be of interest to her and also to others to know that this hospital was opened in October, 1910, and that the public, undeterred by her horror, have thronged to it in such numbers that there have not been beds enough for the several hundreds of disappointed applicants.

An editorial in the Journal of Zoöphily³ records a gift to this Rockefeller Institute, "an institution in New York where vivisection should be practiced with the idea of achieving as great an advance as possible in the war of science against human suffering," and adds, "but the gift only fanned into fury the opposition of the women to experiments on living animals, *no matter how great the anticipated benefit.*" Could cruel passion be better expressed?

Can a cause which so seriously injures the character of its advocates that they indulge in this prolific vocabulary of vituperation by any possibility have an uplifting influence? It eminently fulfills the proposed test — it "hurts the character and, therefore, cannot be right."

Are those who give loose rein to such passion fitted to form a sound and sane judgment on the subject about which they write? This is especially true when the matter is one so technical as anatomic, physiologic, chemical, pathologic and surgical investigations as to

which they cannot be expected to know and, in fact, do not know anything. Even relatively few medical men are fitted by temperament and training to act as censors of such researches, much less those ignorant of medicine.

I believe that much of the passion shown in the above quotations is the result of ignorance. Most of the attacks on vivisection, as I have said, assume or even state categorically that anesthetics are not used. Saving in the very rare cases in which the use of anesthetics would entirely frustrate the experiment, anesthetics are always used. This is done not only for reasons of humanity, but also because the struggles of a suffering animal would make delicate and difficult operations absolutely impossible, to say nothing of the danger of injury to the operator.

The always-quoted opinion of Professor Bigelow was founded on what he had seen at the Veterinary School at Alfort, France, in the preanesthetic days. Many absolutely false statements are made that anesthetics were not used in certain specified experiments, whereas the experimenters have expressly stated that anesthetics *were* used. Of such misstatements by antivivisection authors I shall give some startling instances later. It is no wonder that the public has been thus misled. "Cutting up men and women alive" is an accurate description of every surgical operation, but we all know that while in comparatively few reports of surgical operations it is expressly stated that an anesthetic *was* used, such use "goes without saying."

One of the most frequent antivivisection statements is that "incomplete" or "slight" or "light" anesthesia means that the animal is fully able to feel pain and that when the eye resents a touch or there is muscular movement following any act which would be painful when one is not anesthetized, pain is actually being inflicted. Mr. Coleridge says (Question 10,387 in his testimony before the Second Royal Commission on Vivisection), "What does 'anesthetized' mean? It means 'without feeling.' You cannot be slightly without feeling. You either feel pain or you do not."

Very recently when I had nitrous oxid gas given several times to a lady to bend a stiff elbow she struggled and writhed so hard as almost to throw herself out of the dentist's chair onto the floor. *Yet she was never conscious of the slightest pain.* In other words, while

the motor nervous centers responded to my forcible bending movements and caused violent muscular struggles, the perceptive nervous centers felt no pain. But any spectator would surely have said that she was being "tortured." This is only one of hundreds of similar cases I have had; all other surgeons have had similar experiences.

In modern laboratory researches, ether or other anesthetics are almost always given. Extremely few exceptions occur, and then only with the consent of the director in each specific case. The actual conditions at the present day are well shown by the rules in force in practically all American laboratories of research. These rules have been in operation for over thirty years in one case and for more than ten years in others. In most laboratories in which students work, and where they are absolutely under the control of the director, the only animal used is the frog, and by "pithing" or decapitating it, it is made wholly insensible to pain.

The idea that students privately "torture" animals, often, it is stated, out of mere curiosity, is absolutely false. I have been intimately associated with students ever since 1860, first as a student and since 1866 as a teacher. I state, therefore, what I am in a position to know. Moreover, private experimental research takes time which our overworked students do not have, and money which they cannot afford. It means the rent of a laboratory, the purchase of very expensive and delicate instruments, the rent of an animal room, the cost of the animals, and of their food and care, a man to look after them — for all modern surgical work on animals must be done with the same strict antiseptic care as on man or the experiment will surely fail and discredit the author — a total expense amounting to a very large sum.

I quote in full the rules which, as I have said, are in force in practically all American laboratories of research:

RULES REGARDING ANIMALS

1. Vagrant dogs and cats brought to this laboratory and purchased here shall be held at least as long as at the city pound, and shall be returned to their owners if claimed and identified.
2. Animals in the laboratory shall receive every consideration for their bodily comfort; they shall be kindly treated, properly fed, and their surroundings kept in the best possible sanitary condition.

3. No operations on animals shall be made except with the sanction of the director of the laboratory, who holds himself responsible for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems.

4. In any operation likely to cause greater discomfort than that attending anesthetization, the animal shall first be rendered incapable of perceiving pain and shall be maintained in that condition until the operation is ended.

Exceptions to this rule will be made by the director alone, and then only when anesthesia would defeat the object of the experiment. In such cases an anesthetic shall be used so far as possible and may be discontinued only so long as is absolutely essential for the necessary observations.

5. At the conclusion of the experiment the animal shall be killed painlessly. Exceptions to this rule will be made only when continuance of the animal's life is necessary to determine the result of the experiment. In that case, the same aseptic precautions shall be observed during the operation, and so far as possible the same care shall be taken to minimize discomforts during the convalescence as in a hospital for human beings.

[Signed]
Director of the Laboratory.

I may add that at the Rockefeller Institute regular trained nurses are employed and are on duty not only during the day, but at night when necessary.

Self-confessed total ignorance of a subject on which one gives extensive evidence is not often known, but Dr. Herbert Snow of London, an authority among the antivivisectionists, is a case in point. Dr. Snow's evidence before the Royal Commission on Vivisection (1906) covers ten pages quarto and he answers 326 questions. In 1911 Dr. Snow visited America. In a letter to the Philadelphia *Ledger*⁴ he makes the almost incredible statement that he gave all this evidence "in utter ignorance of the vivisection question."

Moreover, when asked by the Commission (Question 2242), "Do you find any fault with the present gentlemen who are licensed under the act?" he replied, "I do not," and again (Questions 2227 and 2228) he admits that both painful and painless experiments may sometimes be necessary.

In other cases ignorance of physiology and anatomy is shown which would only excite a smile did it not

4. Philadelphia *Ledger*, March 6, 1911.

gravely mislead the reader. I shall give only a single illustration here. Others will be found elsewhere in this paper.

“The Nine Circles,” with its sulphurous subtitle, “Hell of the Innocent,” is an English book originally issued by the late Miss Frances Power Cobbe, in 1892. This edition had to be withdrawn on account of its false statements, especially as to the non-use of ether.⁵ A second and revised edition was issued in 1893. This was “carefully revised and enlarged by a subcommittee especially appointed for the purpose,” as the preface states.

On page 15 of the revised edition, it is correctly stated that Prof. Henry P. Bowditch of the Harvard Medical School, in some experiments on the circulation, etherized a cat and that “then its sciatic nerve was divided, etc.” The sciatic nerve is the largest nerve in the body of man and animals and passes down the back of the leg. After division of the nerve the portion going down the leg *below* the place where the nerve was divided was stimulated by an electrical current. As this part of the nerve was wholly cut off from the spinal cord and brain, *by no possibility could any pain be felt*. Yet a Boston lawyer, in a leaflet published by the New England Antivivisection Society, comments on a similar experiment as follows: “It will be readily seen even by the casual reader that it involves an amount of agony beyond which science is unable to go.” Just how the “casual reader” would be so well informed as to physiology when a lawyer and two doctors—not casual but intelligent and careful readers—got things totally wrong, is not stated. Dr. Bowditch published a correction⁶ of this misstatement in 1896. In spite of this, the New England Antivivisection Society in 1909, *thirteen years* after this public correction, was still distributing this lawyer’s statement.

But in “The Nine Circles” (second edition, carefully revised by Dr. Berdoe and the committee) these experiments are referred to as “experiments on *the spinal cord*”! (Italics mine.) Yet Bowditch did no operation on the spinal cord. Miss Cobbe, not being an anatomist, might be pardoned for confusing the thigh and the spine of the cat, but surely Dr. Berdoe ought to have seen to

5. See pp. 26, 27 and 28 of this reprint.

6. Bowditch, Henry P.: *Advancement of Medicine by Research*, p. 43.

it that "sciatic nerve" and "spinal cord" were not used as interchangeable terms.

Many years ago, after amputating a leg near the hip, I tried to see how long electric stimulation of the sciatic nerve would cause the muscles of the amputated leg to contract. After four hours, during all of which time the muscles continued to react, I had to stop as I could give no more time to the experiment. According to the canons of antivivisection as voiced above, I should have continued to etherize the patient whose leg had been amputated, for he, just as much as Bowditch's cat, could feel "agony beyond which science is unable to go."

Let me give only two other surprising statements. Dr. Hadwen⁷ criticizes my reference in *Harper's Magazine*⁸ to "an astringent named 'adrenalin.'" I had shown how valuable adrenalin had been in saving human life in certain surgical conditions, and also described the resuscitation, by means of adrenalin and salt solution, of a dog which had been "dead" for fifteen minutes. Dr. Hadwen concludes his paragraph thus: "But it does seem a pity that these New World vivisectors will not be able to perform the resurrection miracle without first killing somebody to get at his kidneys." The presumable object of "getting at his kidneys" would be in order to make adrenalin from them. Now adrenalin is *not made from the kidneys at all*, least of all from human kidneys, but from the adrenal glands of animals.

In the same article he vaunts the use of salt solution instead of the direct transfusion of blood, and rightly says that he has "seen the most marvelous effects follow the injection of an ordinary saline solution into the venous system in cases of loss of blood." But he seems to be ignorant of the fact that this very saline transfusion was begun and perfected by experiments on animals. I commend to him Schwarz's essay (Halle, 1881) with its twenty-four experiments on rabbits and dogs, and Eberius' essay (Halle, 1883) with its ten experiments on rabbits and the record of eleven cases in which Schwarz's method had already been used in man. These essays were practically the beginning of our knowledge of the advantages of the use of salt solution over the old dangerous methods of transfusion of blood.

The antivivisectionists deny the truths of bacteriology. Yet we practical physicians, surgeons and obstetricians

7. Hadwen: *Jour. Zoöphily*, January, 1910.

8. Keen, W. W.: *Harper's Magazine*, April, 1909.

know by daily experience that Pasteur's and Lister's researches are the basis of most of our modern progress. Are Hadwen, Harrigan, Snow and their colleagues right and have all medical colleges all over the world in establishing chairs of bacteriology and all medical men in believing bacteriologic diagnosis of such importance and in basing on the germ theory their antiseptic treatment which has so revolutionized modern surgery been wholly wrong? The germ theory is as well established as the doctrine of the circulation of the blood.⁹

II. FOSTERING A SPIRIT OF CRUELTY TO HUMAN BEINGS

My second reason for believing that antivivisection injures character is that, by putting a greater value on the well-being and the lives of monkeys, guinea-pigs, rabbits, dogs, cats, mice and frogs than on the lives of human beings, it fosters a spirit of cruelty to human beings.

Is it not a cruel passion which will lead men and women to write such letters and to print such epithets as I have quoted? Is it a right thing to misstate the facts of operations, and after the falsity of the charge has been proved, still continue for years to hold up men with human feelings and sensitive to abuse before the community as vile monsters of cruelty? Nay, more than this, is it not an extraordinary thing that those who so vehemently denounce human vivisection are even among its advocates?

9. In Mrs. White's answer to this address (*Boston Med. and Surg. Jour.*, July 25, 1912, p. 143), as the editor on page 131 points out, her reference to the "fever inseparable from the healing of abdominal wounds" shows ignorance of the results of modern progress in surgery. Thanks to bacteriology and the antiseptic method of Lister and his followers, thousands of surgeons and patients the world over can confirm my own experience, both as a surgeon and as a patient, that *no* fever usually follows a clean abdominal operation. Before Lister's day, not only was there the terrible fever and suffering of peritonitis, but the mortality was so great that we never dared to do many operations which are now commonplace and rarely fatal. Another illustration of ignorance of surgery is found in Mrs. White's reference (p. 143) in the same paragraph to the "pain caused by the presence of gall-stones in the gall-bladder," a pain which she says "is generally considered the most violent pain known." Now, it is true that sometimes "gall-stones in the gall-bladder" do cause some or even considerable pain; but many post-mortem examinations reveal "gall-stones in the gall-bladder" which have never given the patient the slightest pain, and the patient, therefore, was totally ignorant of their presence. The "violent pain" to which she refers is due not to their presence in the gall-bladder, but to the terrible "gall-stone colic" caused by the passage of the gall-stones out of the gall-bladder into its duct, or tube, opening into the bowel. Modern antiseptic surgery prevents these constantly recurring attacks by safely removing the gall-stones from the gall-bladder or from the gall-duct.

When I was professor of surgery in the Woman's Medical College of Pennsylvania I took as the topic of my address at one of the commencements, "Our Recent Debts to Vivisection." Mrs. Caroline Earle White published "An Answer to Dr. Keen's Address Entitled, "Our Recent Debts to Vivisection." At the bottom of page 4 I find the following: "I take issue with Dr. Keen in the second place where he says, 'These experiments cannot, nay, must not, be tested first upon man.' I assert, on the contrary, that *in the majority of cases they must be tested first upon man* [italics my own] or not tested at all, because no important deductions can ever be drawn with any degree of certainty from experiments upon animals, since in some inexplicable way their construction is so different from that of man."

The statements in the latter portion of the concluding sentence will much amuse anatomists, physiologists and biologists, or, in fact, any one who really knows anything about science. With minor modifications, man and the lower animals are alike in almost all particulars, both in structure and function, in health and disease.

The extraordinary fact is that Mrs. White asserts that experiments must be tested first on men or not tested at all. That is to say, we must either experiment on human beings or else continue in exactly the same old rut as before and never make any progress, for every departure from prior practice, however slight, is an "experiment."

If this basic doctrine of antivivisection had held good for the last fifty years Lister would not have been able, after carefully testing his antiseptic method on animals and having found it successful, then, and not before then, to try it on man.¹⁰ By this means he became, as the *British Medical Journal* has just called him, "the maker of modern surgery."

On page 10 of Mrs. White's "Answer" is found the following flat-footed advocacy of human vivisection: "Dr. Keen mentions that in India alone 20,000 human beings die annually from snake-bites and as yet no antidote has been discovered. How can we search intelligently for an antidote, he says, until we know accurately the effects of the poison? I should reply that in order to find out the effects of the poison and to

10. Keen, W. W.: Modern Antiseptic Surgery and the Rôle of Experiment in Its Discovery and Development, Jour. Am. Med. Assn., April 2, 1910, p. 1104. Reprinted in this series of pamphlets on Defense of Research. See No. XII, page 2 of the cover.

search also for an antidote, the best plan would be for the experimenters to go to India where they could find as large a field for investigation as they require in the poor victims themselves. *Here is an opportunity such as is not often offered for experimenting upon human beings,*¹¹ since as they would invariably die from the snake-bites, *there can be no objection to trying upon them every variety of antidote that can be discovered.* Nothing seems to me less defensible than these experiments on the poison of snake bites upon animals since it is the one case in which they could be observed with so much *satisfaction and certainty upon man!*" (Italics my own.)

Such a proposal is as absurd as it is cruel. Even if the experimenter could afford sufficient time and money to go to India for months or rather for years, how could he arrange to be present when such unexpected accidents occurred? How could he have at hand in the jungle the ether, chemicals, assistants, tables, tents, food and drink, and the necessary yet intricate and delicate instruments? And even if he had all of these, how could he work with the calmness and the orderly deliberation of the laboratory when a fellow human being's life was ebbing away and every minute counted in such a swift poison? The proposal is cruel and revolting and would never be accepted by any investigator.

But Mrs. White is not the only one who is guilty of making such a proposal. Many antivivisection leaflets and pamphlets express the wish that the vivisectors should be vivisected. In a pamphlet¹² freely distributed in the United States I find the following in a letter from a man at that time a Senator of the United States: "It would be much better to dissect men alive occasionally for the general welfare because the attendant phenomena and demonstration of the victims being of our own particular form of animal would be far more

11. In her answer to this address (*Boston Med. and Surg. Jour.*, July 25, 1912, p. 143), Mrs. White, after ample time for reflection, defends her proposal for "experimenting on human beings," saying that "it does not seem to me that this is a cruel suggestion, as my only object in it was to benefit the poor natives who die by the thousand every year." Such a defense places her clearly and definitely among the advocates of vivisection, whose "only object" is to prevent death "by thousands every year." This object, moreover, has already been obtained in a score of diseases and will be obtained hereafter in many others, not, however, by "experimenting on human beings," as she advocates, but on dogs, cats, rabbits, guinea-pigs, mice, frogs, etc.

12. Cobbe, Frances Power, and Bryan, Benjamin: *Vivisection in America*, p. 15.

valuable than the result of our observation upon the physical structure illustrated in the agonies unto death of the helpless creatures around us." The English is as distressing as the proposal is astounding.

Let me give one more illustration of the effect of anti-vivisection in encouraging cruelty.

To-day the plague, cholera and yellow fever no longer terrify Europe or America. What is the reason for this? Primarily and chiefly the discovery of the germs of cholera and of the plague by bacteriologic methods, which in turn are very largely the result of experiment on animals, and of the means of the transmission of yellow fever, though as yet not of its cause. In the latter case experiments on animals were out of the question because it is impossible to transmit yellow fever to animals. They are not susceptible to the poison. So a number of noble medical men and others volunteered to have experiments tried on them. The very first experiments were tried on medical men. These men slept in a stifling atmosphere for twenty nights in the beds in which yellow fever patients had died, and in their very clothes, clothes soiled with their black vomit, urine and feces; tried to inoculate themselves by putting some of the black vomit into their eyes, or by hypodermic injections, etc., but all in vain. By none of these methods were they able to inoculate themselves with the fever. One step more was requisite — to learn whether a well man bitten by an infected mosquito, but having been exposed to no other possible source of infection, would contract the disease. Dr. Carroll of the Army was the first to offer himself, and nearly lost his life. Others followed. Several lost their lives, among them Dr. Lazear, at the beginning of a most promising career. His tablet in the Johns Hopkins Hospital, in the fine words written by President Eliot records that "with more than the courage and the devotion of the soldier, he risked and lost his life to show how a fearful pestilence is communicated and how its ravages may be prevented."

Contrast with this a cruel letter¹³ written by a woman: "Science is based on such firm foundation, indeed, that it can at a moment's notice be tumbled down and become a wrecked mass by a mosquito! Not only this, but these life-long vivisectors could not even prolong

their own lives. Undone by a mosquito! *I shall always have unbounded admiration for that clever insect.*" (Italics mine.)

This self-sacrifice for humanity has made us masters the world over of yellow fever, has made possible the Panama Canal, has saved many thousands of human lives and millions of dollars in our own Southern states alone, and yet a woman can feel "unbounded admiration for the clever insect" which slew these heroes and had devastated cities and countries for centuries! Does not such antivivisection zeal "hurt character"?

Two men are especially obnoxious to the antivivisectionist: Pasteur, whose demonstration of the cause of that form of infection known as puerperal or childbed fever alone would have made his name immortal; and Lister, whose application and extension of the principles laid down by Pasteur have revolutionized all modern surgery.

I need not argue the case for Pasteur, Lister and modern antiseptic surgery. Excepting the antivivisectionists, every intelligent man and woman the world over *knows* that modern surgery has been made safe by their researches. Let me give a single instance.

In the charming "Life of Pasteur" by René Vallery-Radot, it is stated¹⁴ that, hoping to overcome the almost invariably fatal results of ovariotomy in the hospitals, the authorities of Paris "hired an isolated house in the Avenue de Meudon, a salubrious spot near Paris. In 1863 ten women in succession were sent to that house. The neighbors watched those ten patients entering the house, and a short time afterward their ten coffins being taken away!" When I was the assistant to the late Dr. Washington L. Atlee in the late 60's, two patients out of three on whom he, the foremost ovariotomist in America, operated died.

To-day, thanks to Pasteur and Lister and modern surgery, based on experiment on animals more than on any other foundation, not more than two or three in a hundred die after ovariotomy. Yet, if the antivivisectionists had prevailed, the horrible mortality of the earlier days and even the tragedy of the ten women and the ten coffins would still exist. Is not this cruelty?

Let me take another illustration of a similar cruelty, a form especially interesting to women. Prof. J.

14. Vallery-Radot: Life of Pasteur, ii, 16.

Whitridge Williams,¹⁵ professor of obstetrics in the Johns Hopkins University, states the following facts: In 1866 Lefort showed that in 888,312 obstetric cases in the hospitals of France up to 1864, 30,394 women had died of puerperal fever; that is to say, 3.5 per cent., or about every twenty-seventh mother. From 1860 to 1864 the mortality in the Maternité of Paris had risen nearly fourfold, to 12.4 per cent. In December, 1864, it rose to 57 per cent.; that is to say, *more than one-half* of the women who bore children in that hospital in that month died of childbed fever! In Prussia alone, in the sixty years from 1815 to 1875, Boehr showed that 363,624 women had died of the same fever and estimated that every thirtieth prospective mother was doomed to death from that cause. In the United States, Hodge, of Philadelphia, showed that in the Pennsylvania Hospital from 1803 to 1833 there had been a mortality of 5.6 per cent.; i. e., every eighteenth mother was doomed. Lusk reported an epidemic in 1872 with 18 per cent.; that is, almost every fifth mother perished from the same fever!

As late as March, 1879, only thirty-three years ago, at the Paris Academy of Medicine, when the leading men in a debate on childbed fever were at a loss to account for it, Pasteur drew on the blackboard what we now know as the streptococcus and declared this little vegetable organism to be its cause. Our own Oliver Wendell Holmes in 1843 was the first who declared on clinical grounds that the doctors and the nurses carried the contamination, but how and why he could not know, for bacteriology did not then exist. He was followed by Semmelweis, of Vienna, who in 1861 still further reinforced the reasoning of Holmes, and for his pains was tabooed by his professional colleagues and ended his life in a madhouse.

The result of Pasteur's researches and the practical application of Lister's antiseptic method to obstetrics as well as to surgery have borne the most astounding and gratifying fruit. For instance, in 1909 Markoe reported in the New York Lying-In Hospital in 60,000 births a maternal mortality of only 0.34 per cent., and Pinard in 1909 in 45,633 births recorded a mortality of only 0.15 per cent., while in 1907 Mermann had been able

15. Williams, J. Whitridge: *Obstetrics and Animal Experimentation*, *Jour. Am. Med. Assn.*, April 22, 1911, p. 1159, and this series of pamphlets No. XVIII.

to report a mortality of only 0.08 per cent. in 8,700 patients! In other words, these reports show in round numbers that, taking in the two extremes, the deaths from childbed fever fell from the extraordinary rate of fifty-seven in a hundred mothers, or the former usual rate of five or six in every hundred mothers, to one mother in 1,250.

If for fifty years past the antivivisectionists had had their way, all these marvelous results in obstetrics would have been prevented and women would still be dying by the hundred and the thousand from puerperal fever — an entirely preventable disease. Would it not have been the height of cruelty to stop these experiments? But according to the *Journal of Zoophily* such wonderful life-saving experiments should be prohibited, “no matter how great the anticipated benefit.”

In surgery, erysipelas, blood-poisoning, lockjaw, hospital gangrene, etc., would still be killing our patients right and left; weeks of suffering, to say nothing of danger, would confront every patient operated on; the modern surgery of the head, of every organ in the abdomen and pelvis, of tumors and of cancer, amputations and many other operations, instead of being almost painless and so safe as they are to-day, would be the cause of prolonged illness, pain and death; in fact, most of them would be deemed entirely impossible of performance — they *were* impossible before Pasteur and Lister — and animals themselves would still be suffering as of old from animal maladies whose causes are now known and whose ravages have been enormously diminished.

Call you not the desire to arrest such experiments cruelty to man and animals alike?

In a speech in the House of Commons, April 4, 1883, Sir Lyon Playfair, the Deputy Speaker, said:

For myself, though formerly a professor of chemistry in the greatest medical school of this country [Edinburgh], I am responsible only for the death of two rabbits by poison, and I ask the attention of the House to the case as a strong justification for experiments on animals; and yet I should have been treated as a criminal under the present act [the British vivisection law] had it then existed.

Sir James Simpson, who introduced chloroform, . . . was then alive and in constant quest of new anesthetics. He came to my laboratory one day to see if I had any new substances likely to suit his purpose. I showed him a liquid

which had just been discovered by one of my assistants, and Sir James, who was bold to rashness in experimenting on himself, desired immediately to inhale it in my private room. I refused to give him any of the liquid unless it was first tried on rabbits. Two rabbits were accordingly made to inhale it; they quickly passed into anesthesia and apparently as quickly recovered, but from an after-action of the poison they both died a few hours afterward. Now was this not a justifiable experiment on animals? Was not the sacrifice of two rabbits worth saving the life of the most distinguished physician of his time?

As this experiment was not for the good of the two rabbits, but in fact, killed them, in the eye of present-day antivivisectionists it would be wrong, and, if they had their way, illegal and punishable, and Simpson would have lost his life. Would not this be cruelty?

Let me state briefly two of the most recent discoveries in medicine and surgery:

1. Vaccination against typhoid fever. Starting from Pasteur's researches on animal diseases and continued by various observers and especially in the last few years by Sir Almroth Wright, of London, there has been developed chiefly by experiments on animals a "vaccine" to *prevent* typhoid fever. When by such experiments the method was found to be sufficiently safe, it was tried on man.

In the Boer War, and among the German troops in their African colonies, tentative trials of its value were made. Now it has been tried in the United States Army on a larger scale and with more astonishingly good results than in any previous trials.

During the Spanish War there were 20,738 cases of typhoid and 1,580 deaths; nearly *one-fifth of the entire army* had the disease. It caused over 86 per cent. of the entire mortality of that war! In some regiments as many as 400 men out of 1,300 fell ill with it. How this would handicap an army in the field — to say nothing of deaths — is evident.

Lately in our army on the Mexican border, for months under war conditions, except as to actual hostilities, *there has not been a single soldier ill with typhoid*. This is due partly to better sanitation (which in turn is due largely to bacteriology) but chiefly by reason of wholesale antityphoid vaccination. This is evident from the fact that during the year June 30, 1908, to 1909, when this vaccination was purely voluntary and the

army was not in the field, proportionately *sixteen times* as many unvaccinated soldiers fell ill with the disease as compared with the vaccinated. On the Mexican border there has been only one single case of typhoid, not in a soldier, but a teamster who had not been vaccinated. So evident are the benefits of this preventive inoculation that Dr. Neff, the director of health of Philadelphia, has issued a circular proposing its municipal use, and also to prevent typhoid in our summer resorts. In many large hospitals it is extensively used to protect the physicians and nurses from catching the fever.

Would it not have been cruel to prevent such life-saving experiments?

2. In surgery let me instance the surgery of the chest. This has been the region in which progress has lagged far behind that of all the other parts of the body till within the last five or six years. The reason was that the moment you opened the chest cavity to get at the heart, the lungs, the esophagus, the aorta or the pleura, it was like making an opening in the side of a bellows. The air, instead of being drawn in and forced out through the nozzle (corresponding to the mouth in the case of a patient), passed in and out through the opening in the side of the bellows or the chest. If only one side was opened, breathing was embarrassed, if both sides were opened the patient's lungs collapsed, breathing was impossible and death ensued.

Sauerbruch, then of Breslau, first devised a large air-tight box or chamber in which the pressure of the air could be increased or diminished at will. The body of the patient, the surgeons, nurses and instruments were all inside the box, and a telephone enabled them to give directions to those outside, especially to the etherizer. The head of the patient with an air-tight collar around his neck protruded outside of the chamber where the etherizer also was placed. In such a chamber the chest could be safely opened. But while this was an immense improvement, such a chamber is clumsy, not easily transportable, and is very expensive. The method has done good service, however. It has been improved by others and is in use to-day by many surgeons.

At the Rockefeller Institute, Meltzer and Auer, by a number of experiments on animals, have lately developed a new, simple and safe method of anesthesia with ether which is revolutionizing the surgery of the chest and to a considerable extent may even displace the ordinary

inhalation method of anesthesia. As soon as the patient has been etherized in the ordinary way, a rubber tube is inserted into the windpipe through the mouth. By a foot bellows ether-laden air is pumped into the lungs through this tube, the foul breath escaping between the tube and the windpipe and out through the mouth. Experiments on animals showed that the rubber tube used for so long a time would not injure the vocal chords and so alter or destroy the voice of a patient, or cause injury to the lungs, and that the method was most efficacious in the surgery of the chest.

I saw Carrel thus keep a dog under ether for about an hour and a half; open both sides of the chest by one wide sweep of the knife, displace the heart and lungs this way or that; expose and divide the aorta between two clamps (to prevent immediate fatal hemorrhage); do a tedious and difficult operation on the aorta; unite its two cut ends; replace the heart and lungs, and close the wound. An hour later the dog, which showed no evidences of suffering, was breathing naturally, and in time recovered entirely.* What this method means in injuries and diseases of the heart, in gangrene, abscess and tumors of the lungs, in cancer of the esophagus, and foreign bodies lodged in the esophagus or in the bronchial tubes, and in diseases of the aorta, one can hardly yet even imagine.

These experiments have done more for the surgery of the chest in three or four years than all the "clinical observation" of cases in a thousand years. The method has already been tried successfully in several hundreds of cases in man, and the future has in store for us a new and most beneficent chapter in the surgery of the chest.

Yet if the antivivisectionists had prevailed all these experiments would have been prevented, the doors of the Rockefeller Institute nailed up, and men, women and children have been deprived of the benefits of these splendid discoveries. Call you not that intensely cruel?

Moreover, these very same people in their own households and without the slightest pity will kill rats and mice by turning them over to the tender mercies of cats, by drowning them, by strangling them in traps, by poisoning them with strychnine or phosphorus, or by

* For these and other experimental researches Carrel has just been awarded the Nobel Prize in medicine—a splendid testimony to his genius—from the first scientists of the world.

any other means of "torture"; but they hold up their hands in holy horror when any proposal is made to terminate the lives of other rats and mice almost always without pain and with immense benefit to humanity. They are cruel and callous to human suffering so long as dogs and cats, mice and guinea-pigs escape! And yet, as I have shown, only twenty-six animals in a thousand can possibly ever suffer at all!

That sentiment rather than principle is at the bottom of the antivivisection crusade is shown by what I in common with many others believe to be true, that if experimental research could be carried on in other animals without using dogs and cats there would scarcely have been any antivivisection movement.

III. DIMINISHING OF REVERENCE FOR ACCURACY

The third way in which the influence of antivivisection injures character is by diminishing the reverence for accuracy. In 1901 I gave many instances¹⁶ of the misstatements of the antivivisectionists. These misstatements were contained in two anonymous pamphlets, and I have two more similar publications which are also anonymous. I have before me also three publications purporting to be replies to that publication of mine, all again anonymous. Is a foe who attacks from ambush worthy of the respect and confidence of the public?

These misstatements, so far as I know, are still distributed in leaflets and pamphlets without correction nearly eleven years after their incorrectness was shown. In fact, several of them reappear uncorrected in the *Journal of Zoophily* for July, 1911.

Let me give a few new instances.

The most prominent antivivisectionist in England is Mr. Stephen Coleridge. On page 183 (April to July, 1907) in the minutes of his evidence before the Royal Commission on Vivisection, I find the following:

Question 10952: We may have inspection, but still we may ask a person of character when he saw the experiment what his opinion of it was. Will you not accept that?

Answer: Certainly not, because I think that all these experimenters have the greatest contempt for the act of Parliament. They would deny a breach of this act just as I should deny a breach of the motor car act. I drive a motor car and

16. Keen, W. W.: Misstatements on Antivivisection, Jour. Am. Med. Assn., Feb. 23, 1901, p. 500.

when I go beyond the speed limit and the policeman asks me I say, 'No, I am not going beyond the speed limit,' [italics mine]. Nothing would keep me from going beyond the speed limit except the presence of a policeman in the car; and nothing will keep the experimenter within the four corners of the act except an inspector in the laboratory.

Question 10953: Surely, if you were asked about the speed limit and gave your word that you had not exceeded it, you would not expect to be disbelieved?

Answer: No, I did not say so. I said last year that of course I did, and I exceed it every time.

Question 10954: *You are apparently not very ethical about motor cars* [italics mine]. If you apply your principles as regards motoring to the physiologists, you have very little to say against them?

Answer: What I have to say is that they regard the vivisection act of 1876 with the same contempt that I regard the motor car act as regards the speed limit.

In quoting also a letter from the Home Office Mr. Coleridge admits mutilating it, for in reply to Question 11015, he says, "I seem to have left out the important item of it." See also Questions 10301, 11011, 11024 and 19967 to 19973.

Comment on Mr. Coleridge's testimony is superfluous.

Again in the "Black Art of Vivisection," Mr. Coleridge states, "The Pasteur institutes in Paris and elsewhere have entirely failed to prevent people dying of hydrophobia." Yet the fact is that formerly from 12 to 14 per cent. of persons bitten developed the disease and every one of them died, whereas the result of the Pasteur treatment in 55,000 cases has diminished the mortality to 0.77 per cent. of those bitten.

I cite another English instance. In "The Nine Circles,"¹⁸ is published a reply to a letter by Sir Victor (then Mr.) Horsley, published in the London *Times*, Oct. 25, 1892, a copy of which I have before me. The book, as the London *Times* points out in an editorial, was

17. In a letter referring to this address (Boston Med. and Surg. Jour., July 11, 1912, p. 71), Mr. Coleridge says that I seem "quite shocked that he should admit that he constantly breaks the law and exceeds the speed limit of 20 miles an hour in his motor car," and that "a quarter of a million motorists" do the same. If the reader will again peruse Mr. Coleridge's testimony, as quoted in the text, he will find that there are two admissions: (1) that he constantly breaks the law, i. e., the "statute law" of England as to the speed limit; and (2) that when he goes beyond the speed limit, and the policeman asks him he says, "No, I am not going beyond the speed limit." The last statement is what gives special point to the quotation from his evidence, but in his letter he omits any reference to this more important admission.

18. Second Edition, pp. 23-28.

Compiled under his [Dr. Berdoe's] direction. He was entrusted with the task of reading the proofs and was supposed to safeguard the accuracy of "the compiler." He now admits that he overlooked in Miss Cobbe's preface a passage in which she "was careful to say, . . . so far as it has been possible, the use or absence of anesthetics has been noticed in regard to all the experiments cited in this book." Mr. Horsley in the appendix to his letter, which we publish this morning, shows by reference to some twenty cases cited in "The Nine Circles" how entirely inconsistent with the truth this guarantee is, and Dr. Berdoe's reluctant acknowledgment completes the proof.

A still more remarkable letter appears in the same number of the *Times* from Prof. C. S. Sherrington of Liverpool. He says:

I find in the book, "The Nine Circles," three instances in which I am by name and deed held up to public abhorrence. From each of the three statements made about me the employment of anesthesia in my experiments is studiously omitted, although expressly mentioned in each of the published papers on which these statements are professed to rest. In two out of three statements I am accredited with inflicting on living animals, and without the employment of anesthetics, a dissection and procedure that I *pursued only on animals which were dead.*

Accordingly the society withdrew the book from the market, but later published a revised second edition.

In his reply to Professor Horsley's letter calling attention to the misstatements in the first edition, the excuses that Dr. Berdoe gives in this second edition are very extraordinary. Among them, for example, one is "the sentence about testing the sight after recovery from the anesthetic was overlooked.

Another excuse is "this was taken at second hand from another report where the question of pain was not under discussion." In a third he says, "We have not always access to 'original papers' and can only rely on such reports and extracts as are given in the medical and other journals."

I ask whether it is fair, square dealing to base grave charges of cruelty on sentences "overlooked" and on "second-hand" misinformation?

But Miss Cobbe was by no means satisfied with misrepresenting English medical men. In the pamphlet "Vivisection in America," I find on page 9 a letter by a

Boston lawyer in which he says of American experiments, "In other words, animals are dissected alive *usually without the use of anesthetics*, for the supposed (but illusory) gain to science." (Italics mine.) I have already given a table showing that only twenty-six animals out of a thousand could by any possibility have suffered any pain, and that even these were anesthetized. Is it correct, then, to say that animals are "dissected alive usually without anesthetics"?

Near the top of page 45 Miss Cobbe's pamphlet reads as follows:

Dr. Ott, in the *Journal of Physiology*, Vol. II, p. 42, describes a number of experiments on a number of cats *not etherized* [italics my own], for the purpose of making observations on the physiology of the spinal cord.

I find that on reading the original paper there were four series of experiments:

In the first series, there were twenty experiments. In the first experiment the animal was killed before the experiment began. In eleven other instances it is expressly stated in each experiment that the animals *were* etherized. Dr. Ott informs me that the other eight were so etherized and that he invariably etherizes the animals.

In the second series there were eight experiments. On page 52 of the *Journal of Physiology* it is stated that the animals *were* etherized.

The third series consisted of ten experiments, and on page 54 it is expressly stated that the animals *were* etherized.

The fourth series consisted of ten experiments and again on page 60 it is stated that the animals *were* etherized. We see, therefore, that Miss Cobbe's statement "not etherized" is untrue, for of forty-eight animals, one was killed; in thirty-nine it is expressly stated that they were etherized; leaving only eight out of forty as to the etherization of which nothing is said, though it was done.

On pages 45 to 48 I find a series of experiments on the surgery of the pancreas by the late Dr. Senn of Chicago. This was in July, 1886, at a time when the surgery of the pancreas was just beginning. Two pages and a half of Miss Cobbe's pamphlet are devoted to describing in detail experiments which, as no mention is

made in her pamphlet of ether, one would certainly suppose were done without ether and would certainly be very painful. On looking at page 142 of the original paper I find that it is expressly stated that the animals *were* etherized.

In a series of experiments by Halsted, under experiment No. 6, p. 51, Miss Cobbe's pamphlet says, "Died under the operation, which was carried on for two hours on a young, small brindle dog," which would imply two hours of "agony." The original expressly states the fact that this dog died *from the effects of the ether*.

So much for Miss Cobbe's idea of reproducing accurate accounts of the experiments to which she refers.

An amusing instance of misrepresentation is seen in an antivivisection comment made on one of Carrel's experiments on a cat. "How intense the suffering must have been to cause a cat (an animal usually so quiet and reposeful) to spend the day jumping on and off the furniture!" As a matter of fact, the kitten was only "playing with a ball of paper."

Another illustration of the way in which sentences are detached from their context and made to mean quite different things and repeatedly published years after the falsity of the statement has been demonstrated is shown by the constant inclusion of Sir Frederick Treves among the opponents of vivisection. He stated of one single investigation that operations on the intestines of dogs in his opinion — other surgeons do not hold the same opinion — were useless as a means of fitting the surgeon for operations on the human bowel. Ever since this utterance¹⁹ Sir Frederick Treves has been constantly quoted in the manner mentioned, yet in a letter to the London *Times* of April 18, 1902, he says:

The fallacy of vivisection can hardly be said to be established by the failure of a series of operations dealing with one small branch of practical surgery. No one is more keenly aware than I am of the great benefits conferred on suffering humanity by certain researches carried out by means of vivisection.

This was noticed editorially in the *British Medical Journal* of April 26, 1902. So late as 1909, in the May number of the *Journal of Zoophily*, the editor-in-chief, Mrs. Caroline Earle White, reprints from the *North American* of April 12, 1909, her signed letter, and implies that Sir Frederick Treves is an opponent of

19. Treves, Sir Frederick: *Lancet*, London, Nov. 5, 1908.

vivisection, seven years after this correction had appeared. In the number of the same journal for July, 1909, the associate editor of the journal prints a letter of denial from Sir Frederick Treves, and yet so late as the number for March, 1911, p. 177, the same old quotation from Sir Frederick Treves is published in the same journal which twenty-two months before had printed his own letter of denial.^{20, 21}

At the annual meeting of the Research Defense Society Sir Frederick Treves, in referring to the great progress made in the science of medicine, said: "This progress has in the main been accomplished by experiments on animals." Ought not his name hereafter to be omitted from the list of the opponents of vivisection?

A postal card issued by the American Antivivisection Society in Philadelphia (there are several others of the same sort) presents a picture of a large dog with his mouth gagged wide open and his paws tied "without anesthetic." The object of the gag, of course, is to prevent the animal from biting before and while it is being etherized. It is absurd to state that this produces any pain, but a guide at the traveling antivivisection exhibition explained to two of my friends that it was used to *break the jaws of the dogs!* and that this was done "without anesthetics." But in nearly all our surgical operations within the mouth, on the tonsils, cleft palate, the tongue, etc., we employ gags of various kinds to keep the mouth wide open. To show how little annoyance this causes, here is a picture (Fig. 2) of a little girl, 4 years old, my own granddaughter, with a mouth-gag which I have used many times over with children and adults in operations about the mouth. This particular photograph, it will be observed, was taken also "without an anesthetic." It was not necessary to tie her hands and feet as is done with dogs, for the child regarded the whole proceeding of photographing her with her mouth wide open as a "lark," and sat as still as a mouse. Is it necessary to add that her jaw was not broken?

Miss Britton, in her \$300 antivivisection prize essay²² vividly describes an operation (removal of the breasts

20. Just as I had corrected the proof of this paper, April 29, 1912, I received through the mail from Mrs. Caroline Earle White a reprint of her letter of April 12, 1909, with the same misleading quotation, thirty-three months after Sir Frederick Treves' letter of denial had been printed in her own journal.

21. Treves, Sir Frederick: Brit. Med. Jour., July 8, 1911, p. 82.

22. Our Dumb Animals, January, 1910.

of a nursing mother dog) which was *never done at all*. This fictitious operation is described in "The Nine Circles,"²³ again it appears in Dr. Albert Leffingwell's essay, "Is Science Advanced by Deceit," published in 1900. In 1901 Professor Bowditch called Dr. Leffingwell's attention to the fact that no such operation was



Fig 2.—Mouth-gag as used in operations about the mouth.

ever done. In Dr. Leffingwell's collected essays entitled "The Vivisection Question," on page 169 of the second revised edition (1907), there is, in a footnote, a correction admitting that no such operation was ever done, but on page 67 of the same edition, a description of this same operation still appears uncorrected, six years

23. Second Edition, p. 28.

after Bowditch's letter had been received and the mis-statement acknowledged.

• In the Antivivisection Exhibit which was shown in New York, in the winter of 1909-1910, Professor Lee states that there was "an oven heated by gas burners which contains the stuffed body of a rabbit and which the attendant tells you is used for the purpose of baking live animals to death, and this also is performed without anesthetics." Then to add still further pathos, the note at the end of the label on the oven said "gagging, muffling or severing of vocal organs prevents tortured animals giving voice aloud piteously to such terrible suffering." As a matter of fact, "the oven is an apparatus intended for the *incineration of the . . . refuse of a laboratory!*" I might add that it is a constant practice in medicine and surgery now to use various forms of apparatus for the purpose of "baking" an arm, leg or other part of the body, and lately a patient of mine has had her arm "baked" almost daily for weeks at a temperature up to 300° F. with great benefit.

In the exhibit of the American Antivivisection Society in Philadelphia in November, 1911, a portrait of a dog was shown with a large placard stating correctly that the dog had been stolen from its owner and sold to the University of Pennsylvania for experiment. It omitted to state the further fact, which is perfectly well known, that the dog was kept for identification under Rule 1 (page 12), was claimed, identified and turned over to its owner and *not* used for experiment. Such a placard stating half the truth but not the whole truth inevitably leads the public to draw a false conclusion.

The bodies of three dogs were also exhibited, each labeled "The Vivisected Product of a Philadelphia Laboratory." All show gaping wounds; one, in fact, has the entire abdomen and pelvis wide open. Such a condition is utterly incompatible with any research. Surgeons and physiologists when experimenting on animals are necessarily as scrupulously careful in their antiseptic technic as in operations on human beings. Wounds are accurately closed and carefully dressed. Any experimenter leaving wounds wide open and undressed as are those in these dogs would invite failure in every case, and when he published his results and had to confess to a high and needless mortality, he would discredit himself.

One of these dogs shows an absurd operation in the neck. The great blood-vessels from the right and left sides of the neck have been drawn together in front of the windpipe and then tied — a procedure that is unimaginable to any surgeon. Moreover, from the wide-open abdomen and pelvis the following organs have been removed: the stomach, all the large and small intestine, except a portion a few inches long, the spleen, the pancreas, both the kidneys and the bladder. The liver, however, is left. Cannot even any non-medical person of ordinary intelligence see that if all these organs were really removed and, in addition, the great blood-vessels of the neck on both sides were really tied, thus cutting off almost all of the blood-supply to the brain, and then the neck and the abdomen were left wide open, the death of the animal on the table would be inevitable?

About a dozen medical men, all teachers in medical schools, after careful inspection of these dogs, unite in believing that all or nearly all of these mutilations must have been done post mortem and not during life. Moreover, there is no *evidence* that these animals were really "vivisected," that is, operated on during life.

Still further, granting that all these operations were done for research and during life, if the animals were etherized no pain would have been felt and no cruelty perpetrated. The significant omission to say anything as to any anesthetic, like the omission as to the restoration to its owner of the stolen dog, entirely misleads the public.

Dr. Henry P. Bowditch²⁴ quotes an extraordinary statement of the late Henry Bergh, an ardent antivivisectionist. Mr. Bergh says:

Robert MacDonald, M.D., on being questioned, declared that he had opened the veins of a *dying person*, remember, and had injected the blood of an animal into them many times and had met with brilliant success. In other words, this potestate has discovered the means of thwarting the decree of Providence when a person was dying, and snatching away from its Maker a soul which He had called away from earth.

I have happily been able to rescue quite a number of dying persons who but for my timely aid would have been dead persons. Instead of supposing that I had "thwarted the decrees of Providence and snatched a soul from its Maker," I have always been under the

24. Bowditch, Henry P.: *Animal Experimentation*, p. 72.

impression: (1) that it was not in my feeble power to thwart the decrees of the Almighty, and (2) the very fact that I was able to save a dying person from death was the best evidence that the decree of Providence was that the patient at that time should live and *not* die.

But it seems that in the catechism of antivivisection it is an impious crime to save the life of a *dying* person, though I suppose it is proper to save the life of a patient who is only "sick."

In the *Journal of Zoophilic* for April, 1910, p. 44, under the caption "Still More Barbarity," is an editorial signed "C. E. W.," the initials of the editor-in-chief. In this editorial it is stated as to certain experiments of Dr. Wentworth of Boston that they were "upon between forty and fifty little children in the Children's Hospital of that city, every one of whom died after the performance of his operation." The "casual reader" would certainly understand that every one of these forty to fifty children died as a *result* of the operation.

Let us see what the *real facts* are.²⁵ In 1895, in a case of possible tuberculous meningitis, Dr. Wentworth did lumbar puncture in order to make a positive diagnosis. Lumbar puncture consists in introducing a rather long hypodermic needle between the vertebræ in the small of the back (lumbar region) and withdrawing some of the fluid from around the spinal cord. This fluid circulates freely to and fro both within the brain and its membranes and within the membranes of the spinal cord. The needle is inserted below the end of the spinal cord, rarely with general anesthesia, sometimes with local anesthesia of the skin, but generally without even this, as the pain is slight and only momentary.

In 1895 this method of diagnosis was comparatively new. Its value was uncertain, its dangers, if any, were not determined. The appearance of the fluid and the nature of its microscopic contents in human beings were imperfectly known. Dr. Wentworth in this case used the method for diagnosis. Alarming symptoms appeared, but passed away. The child was proved not to have meningitis and "left the hospital shortly afterward perfectly well."

In order to determine whether this case was exceptional, and the dangers only accidental, or always to be feared (which if true might compel the entire abandon-

25. Boston Med. and Surg. Jour., Aug. 6 and 13, 1896.

ment of lumbar puncture), he repeated the operation most cautiously at first and finally with surer faith in its safety and value in twenty-nine other cases. In fifteen of the thirty cases the puncture was expressly done in order to make a diagnosis — meningitis or other diseases of the brain and spinal cord being suspected. In the other fifteen cases, while there probably was no cerebral or spinal disease, it was of great importance to know whether examination of the cerebrospinal fluid might throw any unexpected side-light on these diseases, and if not, it would at least disclose what the normal condition, appearance and microscopic contents of the fluid were.

Forty-five punctures in all were made on the thirty children. In three cases the puncture was made after death. Of the twenty-seven living children, fourteen died. *Not one of the fourteen died from the operation*, but, as the post-mortems showed, from meningitis, tuberculosis, pneumonia, water on the brain, convulsions, etc., as is expressly stated in each case in the paper.

But the editorial says "between forty and fifty little children . . : . *every one of whom* died after the performance of the operation. I have before me several antivivisection pamphlets published in New York, Philadelphia and Washington in which Wentworth's cases are narrated as cases of "human vivisection," and it is usually stated that "many of them died," but the reader would still suppose that it was as a result of the operation. In two of these pamphlets, "brief abstracts" of five cases are given, usually only one to three lines long. The post-mortem reports published in Wentworth's paper showed that these five patients died from meningitis (two cases), infantile wasting, tuberculosis and defective development of the brain and convulsions. Yet the "casual reader" would inevitably suppose that they died from the lumbar puncture as no other cause of death is stated in these pamphlets.

When Dr. Cannon pointed out the inaccuracy of the editorial of April, 1910, in the *Journal of Zoöphily*, that same journal in the issue for July, 1911, p. 219, in a paper signed "M. F. L." (the initials of its associate editor) not only did not acknowledge the error, but practically repeated it by saying that Dr. Cannon is "severe on the *Journal of Zoöphily* for having referred last year to Dr. Wentworth's forty-five experiments on

children and for having mentioned the fact that *the children died after the operation.*" (Italics mine.)

Is it fair dealing to give such very brief abstracts and omit the most important facts as is done here? In 1901 I pointed out²⁶ these misstatements and what the truth was, but the same pamphlets have been constantly distributed without any correction. In November, 1910, nearly ten years after I had exposed the matter, Dr. Cannon states that one of these pamphlets was sent to a friend of his with a letter from the president of the New York Antivivisection Society, saying, "You may rely on them as being absolutely accurate and authentic!" Still worse: In April, 1910, "C. E. W." enlarges the number from thirty to "between forty and fifty" and actually says that "every one" of them died, and "M. F. L." practically repeats the misstatement by saying that "the children died after the operation."²⁶

Suppose thirty friends dined together at the Bellevue-Stratford, then took a train and as a result of a collision fourteen were killed; would a reporter, and still less an editor, be justified in stating in print "between forty and fifty friends dined last night at the Bellevue-Stratford. Every one of them died shortly after partaking of the dinner" entirely omitting the collision as the real cause of death?

Now after fifteen years, what has been the result of these investigations by Dr. Wentworth and others? Lumbar puncture is a thoroughly well-established means of diagnosis. That it is attended with practically no danger is shown by the fact that it is now a routine practice in certain diseases, even much more important than recording the pulse and the temperature. Holmes²⁷ states that he has done the operation "over four hundred times and has never met with an accident."

It is not only always done in some diseases, but is repeated two, three or more times in the same patient in cases of cerebrospinal meningitis. As I showed in my paper in the *Ladies' Home Journal* (April, 1910) the

26. In Mrs. White's reply to this address (p. 144) she "pleads guilty" to the charge of misstating, as to these children, "that they all died," and says she "unconsciously exaggerated." On page 143 she states that she is "most particular to avoid not only falsehood, but even exaggeration." It is hardly correct to say that the statement that there were "between forty and fifty children" and that "they all died" is an "exaggeration" of the real fact, namely, that there were only twenty-seven living children operated on, and of the fourteen who died *not one* of them died from the operation, but from well-known causes revealed by the post-mortem examinations and fully stated, in each case, in Dr. Wentworth's paper.

27. Holmes. Arch. Pediat., October, 1908, p. 738.

son of then governor, now Mr. Justice Hughes, of the United States Supreme Court, a student at Brown University, stricken with a violent attack of the epidemic form of the disease, had lumbar puncture done three times; the first time in order to make a diagnosis and also for the injection of Flexner's serum, the second and third times for two other injections of the serum, which snatched him from otherwise practically certain death.

In this disease, Royer²⁸ says: "It is absolutely necessary to do a lumbar puncture" to make a diagnosis, and Dunn²⁹ says emphatically, "Without lumbar puncture a diagnosis of cerebrospinal meningitis is absolutely without value for scientific, statistical or therapeutic purposes." As there are half a dozen different forms of meningitis, and the remedy for the deadly epidemic form is of no use in the other forms, lumbar puncture, the only absolutely positive means of differentiating them, cannot be dispensed with.

Moreover, its use has been broadened, as shown in the case of young Mr. Hughes. No longer are we content to use it merely as a means of diagnosis, but it is the only means of successful treatment of that terribly fatal malady. It is also used for diagnosis in several surgical diseases and injuries. Moreover, the method of spinal anesthesia, which is most useful in cases in which other methods of anesthesia are too dangerous, is exclusively by means of lumbar puncture, the cocaine or other local anesthetic being injected around the spinal cord by the hypodermic syringe.³⁰

When a witness is called, it is not allowable for the party calling him to accept a part of his testimony and refuse to accept the rest, yet this is precisely what the opponents of research do. They always cite, for example, the late Professor Bigelow, printing his earlier utterances based on the suffering he saw at Alfort in the preanesthetic days, but they carefully omit the following later expression of opinion:³¹

28. Royer: Arch. Pediat., October, 1908, p. 729.

29. Dunn, Charles Hunter: Am. Jour. Dis. Child., February, 1911, p. 95.

30. Those who wish to consult by far the best statement for general use of the steps by which epidemic meningitis has been conquered and the results of the new but now thoroughly well-established serum treatment by lumbar puncture can obtain a copy of Dunn's paper on this subject (No. 21 of this series) by enclosing 4 cents (or 50 cents for twenty-five copies) to the Journal of the American Medical Association, Chicago.

31. Bigelow, Henry J.: Anesthesia: Addresses and Other Papers, Boston, 1900, p. 371.

The dissection of an animal in a state of insensibility is no more to be criticized than is the abrupt killing of it, to which no one objects. The confounding of a painful vivisection and an experiment which does not cause pain—either because the animal is under ether, or because the experiment itself is painless, like those pertaining to the action of most drugs, or because it is a trivial one and gives little suffering—has done great damage to the cause of humanity, and has placed the opponent of vivisection at a great disadvantage. . . . A painless experiment on an animal is unobjectionable.

So, too, when the statements of Horsley, Ott, Crile and others that the animals were anesthetized and suffered no pain are shown to antivivisectionists, they reply, "We do not believe it, for the only testimony to this insensibility to pain is that of the vivisectors themselves." They greedily accept as true all their other statements as to the operations they did, etc., down to the minutest details, but they refuse to accept those as to anesthesia. No court of law would sanction such a course.

In reviewing the preceding misstatements and those quoted in my former paper¹⁶ I have been compelled to conclude that it is not safe to accept any statement which appears in antivivisection literature as true, or any quotation or translation as correct, until I have compared them with the originals and verified their accuracy for myself. Not seldom this is impossible, as no reference to the volume, month, day or sometimes even the year of publication is given.

Lest the reader think this too severe a statement I will refer to only one instance in the anonymous pamphlet, "Human Vivisection," in addition to others already shown to be grossly inaccurate.

On page 9 in the account of Sanarelli's five experiments in the endeavor to inoculate yellow fever, the phrase "the final collapse" appears as an alleged translation of the original Italian. The word "*final*" does not occur in the original. Moreover, the collapse was not "final," for every one of the five patients recovered, yet the pamphlet says that "some if not all of them died." The phrases "scientific murder" and "scientific assassination" are also freely used. Even the cover and the title-page of this pamphlet have as a motto, "Is scientific murder a pardonable crime?" As not a single patient died, were they really "murdered" or "assassinated"?

CONCLUSIONS

In thirty years the sixteen [British] antivivisection societies have received more than £100,000 (\$500,000) according to Mr. Stephen Coleridge's testimony before the Royal Commission on Vivisection (Questions 10256 to 10260). The American societies have had many bequests given to them, and in the aggregate must have also spent a large sum of money.

On the other side, the friends of research and progress have had little money, have had to stop research and waste a deal of precious time in defending their beneficent researches from the attacks of the antivivisectionists; the rest of the time they have quietly gone about their business, adding to the sum of our knowledge and forging new and more efficient weapons against disease and death.

What, then, is the net result? What have the friends of research accomplished, and what achievements can the foes of research show? Let me put it in a contrasted tabular form and confine it to what has occurred during my own professional life.

THE ACHIEVEMENTS OF THE FRIENDS OF RESEARCH

1. They have discovered and developed the antiseptic method and so have made possible all the wonderful results of modern surgery.
2. They have made possible practically all modern abdominal surgery, including operations on the stomach, intestines, appendix, liver, gall-stones, pancreas, spleen, kidneys, etc.
3. They have made possible all the modern surgery of the brain.
4. They have recently made possible a new surgery of the chest, including the surgery of the heart, lungs, aorta, esophagus, etc.
5. They have almost entirely abolished lockjaw after operations and even after accidents.
6. They have reduced the death-rate after compound fractures from two out of three, i. e., sixty-six in a hundred, to less than one in a hundred.
7. They have reduced the death-rate of ovariotomy from two out of three, or sixty-six in a hundred, to two or three out of a hundred.
8. They have made the death-rate after operations like hernia, amputation of the breast and of most tumors a negligible factor.

9. They have abolished yellow fever — a wonderful triumph.³²

10. They have enormously diminished the ravages of the deadly malaria, and its abolition is only a matter of time.

11. They have reduced the death-rate of hydrophobia from 12 or 14 per cent. of persons bitten to 0.77 per cent.

12. They have devised a method of direct transfusion of blood which has already saved very many lives.

13. They have cut down the death-rate in diphtheria all over the civilized world. In nineteen European and American cities it has fallen from 79.9 deaths per hundred thousand of population in 1894, when the antitoxin treatment was begun, to nineteen deaths per hundred thousand in 1905—less than one-quarter of its death-rate before the introduction of the antitoxin.

14. They have reduced the mortality of cerebrospinal meningitis from 75 or even 90 odd per cent. to 20 per cent. and less.

15. They have made operating for goiter almost perfectly safe.

16. They have assisted in cutting down the death-rate of tuberculosis by from 30 to 50 per cent. for Koch's discovery of the tubercle bacillus is the cornerstone of all our modern sanitary achievements.

17. In the British Army and Navy they have abolished Malta fever, which in 1905, before their researches, attacked nearly 1,300 soldiers and sailors. In 1907 there were in the army only eleven cases; in 1908, five cases; in 1909, one case.

18. They have almost abolished childbed fever, the chief former peril of maternity, and have reduced its mortality from five or ten up even to fifty-seven in every hundred mothers to one in 1,250 mothers.

19. They have very recently discovered a remedy which bids fair to protect innocent wives and unborn children, besides many others in the community at large, from the horrible curse of syphilis.

20. They have discovered a vaccine against typhoid fever, which among soldiers in camps has totally abolished

32. Mrs. White in her letter (p. 144) argues that this statement is incorrect because, forsooth, yellow fever "is still flourishing in a number of places in South America, Central America and Mexico." Of course it is, but all the world knows that if they adopted the methods of Colonel Gorgas in the Canal Zone, yellow fever would soon be banished from these other places. Since May 17, 1906 (now [October, 1912] almost six and a half years ago), not a single case of yellow fever has originated on the isthmus!

typhoid fever, as President Taft has so recently and so convincingly stated. The improved sanitation which has helped to do this is itself largely the result of bacteriologic experimentation.

21. They are gradually nearing the discovery of the cause, and then we hope of the cure, of those dreadful scourges of humanity, cancer, infantile paralysis and other children's diseases.

Who that loves his fellow creatures would dare to stay the hands of the men who may lift the curse of infantile paralysis, scarlet fever and measles from our children and of cancer from the whole race? If there be such cruel creatures, enemies of our children and of humanity, let them stand up and be counted.

22. As Sir Frederick Treves has stated, it has been by experiments on animals that our knowledge of the pathology, methods of transmission and the means of treatment of the fatal "sleeping-sickness" of Africa has been obtained and is being increased.

23. They have enormously benefited animals by discovering the causes and in many cases the means of preventing tuberculosis, rinderpest, anthrax, glanders, hog cholera, chicken cholera, lumpy jaw and other diseases of animals, some of which also attack man. If the suffering dumb creatures could but speak, they too would pray that this good work should still continue unhindered.

THE ACHIEVEMENTS OF THE FOES OF RESEARCH

Not a single human life has been saved by their efforts.

Not a single beneficent discovery has been made by them.

Not a single disease has been abated or abolished by them.

All that they have done is to resist progress — to spend \$500,000 in thirty years in Great Britain alone, and very large amounts of money in the United States —and to conduct a campaign of abuse and gross misrepresentation.

They apparently care little or nothing for the continued suffering and death of human beings, the grief and not seldom the ensuing poverty of their families, provided that twenty-six out of every thousand dogs and cats, monkeys and guinea-pigs, mice and frogs experimented on shall escape some physical suffering.

They insist, therefore, that all experimental research on animals shall stop and — astounding cruelty — that

thousands of human beings shall continue year after year to suffer and to die.

The Age of Experiment is the Age of Progress. This is true in mechanics, in engineering, in electricity, in every department of human knowledge in which experimental investigation is possible.

Medicine is no exception. Stop experiment and you stop progress. But while stopping progress in other departments only means that we shall have no further development in the external comforts and conveniences of life, the arrest of the experimental method in medicine means that progress in the knowledge of the cause and cure of disease shall stop and that our present sufferings and sorrowful bereavements from the onslaught of cancer, scarlet fever, measles, whooping-cough and all the other foes of health and life — especially of our dear children — must continue.

In the last fifty years we have made more progress than in the preceding fifty centuries. I believe that if experimental research is continued and aided, the next fifty years will be still more prolific of benefit to mankind than even the past fifty.

I have absolute confidence in the humanity, the intelligence and the common sense of this nation that they will see to it that this progress shall *not* be halted by the outcries and misstatements of the antivivisectionists.

Dr. S. Weir Mitchell, when visiting the Antivivisection Exhibition in Philadelphia, put the matter in a nutshell when he said to one of the guides, "Your exhibition is not quite complete. You should place here a dead baby and there a dead guinea-pig with the motto, "Choose between them."³³

33. Of course, not all antivivisectionists are to be grouped with those who are responsible for the letters, the epithets and the persistent misstatements mentioned in this paper. I have, for example, some most esteemed personal friends who are more or less opposed to research by means of experiments on animals. But I believe that most of the reasonable persons who take this stand are not well informed, either as to the character of such researches, to their profound importance to the human race and to animals, or to their wonderfully beneficent results. They are misled by the misstatements of the chief antivivisectionists, and their kindly hearts are so shocked by the asserted "torture" of dogs, cats, etc., that they lose sight of the real and horrible torture inflicted on human beings by diseases which the advocates of research are endeavoring to banish. Had they ever stood as in the past I have stood, knife in hand, by the bedside of a gasping livid child struggling for breath, ready to do a tracheotomy when the surely tightening grip of diphtheria made it necessary to interfere, they would hail with delight the blessed antitoxin which has abolished the knife and enormously diminished the mortality of that curse of childhood. They would surely bless God that such a discovery as this antitoxin could be made *solely by experiments on animals*. The sufferings of a few such animals is as nothing compared with the lessening of suffering and saving of life for multitudes of human beings (to say nothing of the saving of sorrow and suffering to their families and friends), not only now, but for all time to come.



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Antivivisection Legislation: Its History, Aims and Menace

W. B. CANNON, M.D.
BOSTON

DEFENSE OF RESEARCH PAMPHLET XXV

Issued by the Bureau on Protection of Medical Research
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the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—*Charles W. Eliot.*

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
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ANTIVIVISECTION LEGISLATION: ITS HISTORY, AIMS AND MENACE*

W. B. CANNON, M.D.

BOSTON

The early triumphs of experimental biology, about the middle of the last century, led to its rapid development as a means of advancing knowledge of physiology, bacteriology, pathology and, later, of other medical sciences. Accounts and rumors of experiments on animals soon aroused fears that many cruel and needless operations were being performed. In Great Britain popular clamor, stirred by the energy of a group of doctrinaires, culminated in the appointment, in 1875, of a royal commission to investigate and report the conditions under which animal experimentation was being conducted. So little had the sciences of pathology and bacteriology profited at that time by use of the new method that physiology almost alone was on trial at the hearings. In spite of this limitation of evidence the strong testimony forced the commission to conclude that abolition of animal experimentation, conducted to mitigate human suffering and prolong human life, would be impossible; and the commission therefore recommended a law licensing proper persons to engage in the practice, ensuring the avoidance or minimizing of pain, and providing for inspectors "of such character and position as to command the confidence of the public no less than that of men of science."

A writer in *Nature*, at that time (1876, p. 248), characterized this recommendation and its result in legislation as follows: "The evidence on the strength of which

* This paper is one of the series prepared for and reprinted by the Bureau for the Protection of Medical Research of the American Medical Association for circulation among the public. Twenty-five of these pamphlets are now ready, taking up the relations of animal experimentation to ethics, diagnosis, cancer, vaccination, the live stock industry, tuberculosis, typhoid, dysentery, plague, rabies, surgery, internal secretions, the circulation of the blood, protozoan tropical diseases, etc.

legislation was recommended went beyond the facts, the report went beyond the evidence, the recommendations beyond the report, and the bill can hardly be said to have gone beyond the recommendations, but rather to have contradicted them." Some of the most objectionable features of the bill, according to Sir Michael Foster,¹ were added as it was being passed through committee in Parliament.

The result of this measure has been that all British experimenters work on ticket of leave. The securing of the ticket is a slow process because of the large amount of red tape involved. In consequence, sudden or unexpected opportunities for research cannot be utilized. And if in the course of an investigation a new line of inquiry is suggested — an event which is often the most valuable and significant phase of the investigation — the ticket must be amended or a new ticket must be secured, to permit work in the new direction, and that means further delay and vexation and cooling of enthusiasm. Furthermore, for some experiments, securing a ticket is so hopeless that investigators must leave their work incomplete or go abroad in order to be permitted to pursue it. Study of the effects of snake-bite, for example, and search for antidotes — a matter of great importance to India because of the high mortality therefrom — had to be suspended in Great Britain because of the British act of 1876.²

One might suppose that, having secured such a degree of restriction of experiments on animals, the antivivisectionists would have rested content. Quite the contrary, however. Agitation against animal experimentation has nowhere else in the world been so violent and so continuous as in Great Britain during these past thirty-six years. In 1906, thirty years after the British antivivisection act was passed, the clamor and constant agitation led to the appointment of a second royal commission. After a very exhaustive inquiry, and after four years of study of the testimony, the commission reported that the scientific investigators, with rare exceptions, have "endeavored, with loyalty and good faith, to conform to the provision of the law," and that "the harrowing descriptions and illustrations of operations inflicted on

1. See letter in Hearing on a Vivisection Bill (S. 34), Senate Committee on District of Columbia, Washington, 1900, p. 99.

2. Minutes of Evidence, Royal Commission on Vivisection, 1907. Question 6833.

animals, which are freely circulated by post, advertisement or otherwise, are in many cases calculated to mislead the public." The second commission merely suggested a few minor changes in the law, all of them within the province of the administration, and not requiring amendment of the act by Parliament.

I have reviewed in some detail the conditions in Great Britain, because they offer an example for us. In spite of drastic legislation, which, as a "penal measure" (it was thus referred to at the time of its passage), placed scientific investigation under suspicious surveillance, antivivisection societies have multiplied, their activities have been unrestrained, and their aims now are avowedly the total abolition of what has proved to be the most fruitful mode of progress in the medical sciences. Thus the passage of legislation in Great Britain has, on the one hand, hampered and limited the efforts of investigators, and, on the other, utterly failed to satisfy the demands of the antivivisectionists.

The reason for the two parties being irreconcilable, the reason for compromise being impossible, lies fundamentally in a difference of moral emphasis. No longer is it the main contention of the antivivisectionists that the use of animals for medical research is unprofitable, though that argument, strange to say, is still heard; they now take what they call "higher ground" and say that their opposition is based on the great moral wrong involved in the sacrifice of animals for man. As one of their witnesses stated, "I would not have one mouse painfully vivisected to save the greatest of human beings, or the life dearest to me." And recently a writer, in the *Philadelphia Journal of Zoophily* (December, 1912), has declared, "Vivisection is utterly detestable. It is immoral and demoralizing. Antivivisectionists should keep up an unceasing agitation and work unitedly in asking legislatures for laws of an entirely prohibitory character." All the antivivisection societies of Great Britain, and all but two or three of the societies in this country, exist expressly for the purpose of abolishing utterly operations on animals for medical and biological research.

The opposite moral attitude, that taken by the investigators, was expressed by the second British commission. Basing their judgment on the "average moral sense of Christian communities," which is "not offended by the sacrifice of lower animals for the food, clothing, adorn-

ment and, within limits, the sport of man," they concluded that properly conducted experiments on animals "are morally justifiable and should not be prohibited by legislation."

Although most antivivisectionists are ultimate abolitionists, and although some among them vigorously denounce merely restrictive legislation as a wicked compromise, which will seriously endanger the securing of their real aim, yet others among them have been quite ready to obtain any legislation whatever to which they might point as a mark of progress. Any sort of specious argument may be expected, when some legislation, even the most trivial and insignificant, is all that is wanted at first. Thus antivivisectionists have declared that their prime object is to stop the abuse of animals by ill-trained physicians, or by raw medical students, operating in private rooms, and that expert investigators and physicians interested in the promotion of medical research ought to be therefore strong supporters of their endeavors. Before this argument is accepted a review of the attempts to obtain restrictive legislation in this country will be instructive.

The most energetic and persistent efforts to have restrictive laws enacted have been made in Massachusetts, New York, and Pennsylvania. I am best acquainted with the agitation in Massachusetts. Seventeen years ago there was presented to the Massachusetts legislature a relatively drastic bill aimed at the limitation and supervision of the experimental use of animals. At the first hearing the crowd was so great that the largest committee room was not large enough, and the meeting had to be adjourned to the old hall of representatives. The petitioners for legislation were ably represented by counsel. The remonstrants appeared as laboratory workers and practitioners of medicine and surgery to testify to what they knew and give reasons for objecting to the proposed bill. After several hearings the committee, convinced of the needlessness of any such bill, voted unanimously that the petitioners be given "leave to withdraw." Then came the sequence of "milder" bills. Attempts with these "milder" bills were made almost every year for the next decade.

During all these later years the laboratory workers conducted their own case; the petitioners were represented by able counsel; invariably the committee refused

to report the bill. There was never any popular demand for legislation; interest was kept alive solely by the efforts and money of a few agitators. The number of petitioners attending the hearings gradually dwindled until, at the last, only their hired lawyer and a few elderly ladies constituted the remnant of the great crowd that came in 1896. Every victory for freedom of research made another victory easier, and just because committees again and again had found no reason to enact restrictive legislation, and because at each successive attempt the petitioners could advance no new arguments, it became always more possible to point to the fate of previous bills as a precedent to follow. In other words, the efforts of the antivivisectionists became classified in the legislative mind as chronic and unjustifiable.

In the course of these repeated hearings the most effective way of presenting the medical and biologic view was gradually developed. It consisted, towards the last, of the testimony of representatives of the educational institutions of the state, the colleges, medical schools and separate biologic laboratories, representatives of the several branches of the medical sciences, representatives of the state and city boards of health, representatives of the cattle bureau, representatives of hospitals, and prominent physicians and surgeons — in short, persons who knew thoroughly every interest that would be seriously affected by limitation of the use of animals for instruction and research. One person was selected to speak for each of the interests concerned and he was limited to ten minutes. Thus the objections to the bill were described to the committee in a series of brief, pointed speeches, so diverse in style and personality as to hold close attention. At the end the leader of the remonstrants summed up the general objections to the proposed bill and answered any arguments that previous speakers might have left untouched.

The history of the agitation in Massachusetts has been repeated in New York. The money of a few individuals has purchased the services of lawyers and a public speaker; and with this subsidized enthusiasm and with the aid of a newspaper made hostile because its disreputable advertising was stopped by the action of a local medical society, the small group of antivivisectionists began their usual tactics. Through pamphlets, leaf-

lets, exhibits, special articles and lectures they thoroughly misrepresented the methods and the results of animal experimentation, until they obtained a considerable following of kind-hearted people who believed that the atrocities they described were actually being perpetrated within the confines of the state. Along with this misleading effort to rouse a detestation of the methods of medical research, the antivivisectionists tried to secure laws of a hostile character. Numerous fruitless attempts were made to enact restrictive bills, each less drastic and more plausible than its predecessors, and then, with steadily diminishing interest at the hearings they took a final step downward in their demands and are now asking for a commission of inquiry. This is the mildest and apparently the most reasonable request that they have made. Who is not appealed to by the call for an "open door"? But this request is supported by the same persons who formerly urged outright antivivisection bills and by some who, in their publications, advocate that animal experimentation be abolished. The present effort, therefore, is merely another attempt to get legislation started in one state so that it may be an example to others. There is no general demand for such investigation; it is assumed in the call for an "open door" that the doors of laboratories are now shut against experienced persons (which is untrue); and the conduct of the investigation is placed not with judicially-minded persons, but with persons some of whom are committed in advance to an antagonistic attitude. Again the British experience may properly be cited to show the futility of attempting to secure any respite from abuse and vituperation by bending to the wishes of persons who are intent on doing their utmost to harass and impede the progress of medicine.

Experience in Massachusetts, New York and elsewhere has not only revealed the main provisions likely to be found in antivivisection bills, but has also brought forward the chief objections to these provisions. A brief summary of these points will be instructive:

1. *Experimentation is restricted to registered buildings.* This is impracticable, in the case of medical emergencies in country places, and would entail difficulties in experiments on diseases of animals used on farms, and of game animals, and hence would be inimical to the farmers and sportsmen of a state. In Great Britain por-

tions of grouse-moors have been necessary for the study of "grouse disease." And Pasteur's proof of immunization against anthrax was made in field operations remote from his laboratory in Paris.

2. *Experimentation is restricted to the purpose of discovering new facts useful in saving or prolonging life or alleviating suffering.* This provision prohibits the use of animals (on the way to death in anesthesia) for the acquirement of technical skill. Thus persons training to practice surgery, for example, would be forced strictly to obtain their first experience by operating (or experimenting!) on human beings instead of the lower animals.

Furthermore, the provision abolishes the use of animals for teaching and demonstrating the methods and facts of physiology, and of all the other experimental biologic sciences, however free from pain these uses are. And, as is generally recognized, to learn to judge the functions of the body by studying inactive structure alone would be like learning to take the responsibilities of an engineer by examining an idle locomotive.

3. *The animal experimented on must be under a general anesthetic.* Often quite as effective anesthesia is produced by a local as by a general anesthetic and, furthermore, much less discomfort is likely to attend local anesthesia and there is no distress in recovering from it. Restricting experimentation to animals under general anesthesia, furthermore, prevents any attempt at finding new anesthetics, and thus either definitely limits mankind to those now employed, or requires the first tests to be made on human beings.

4. *Animals must be killed before recovering from anesthesia.* This process stops absolutely all work in experimental surgery, and in the application of surgical methods in physiology and pathology. If this condition had been enforced during the past fifteen years, some of the most valuable advances in medicine would have been rendered wholly impossible.

5. *Every experimenter must make a report in writing, at certain times each year, stating the nature and results of his studies.* The compulsory reports of all experiments would probably have as their only practical result ignorant prosecutions, followed by acquittal. Nothing is more evident in antivivisection literature than the inability of persons equipped mainly with ignorance and prejudice to read with understanding the technical reports of experts. Misunderstanding necessarily ensues.

It is against sound public policy to discourage legitimate experimental work by the prospect of such prosecutions.

Still another objection to compulsory reports is the danger to the community which might result from the premature publication of insufficiently tried methods of treating disease. Koch's forced premature publication of the action of tuberculin may serve as an instance, but more recent instances are not lacking. Cruelly false hopes, bitter disappointments, the spending of large sums uselessly in traveling far to seek relief from disease or to avoid death—such are the evil results that may flow from compulsory publication.

6. *Laboratories in which animal experimentation is being performed shall be open to inspection by authorized agents.* (Sometimes the bill specifies that these agents shall represent humane societies.) This provision has always met strong opposition—opposition which must be clearly defined, because it is usually taken by the antivivisectionists as a confession of fear of detection in cruel deeds. To this innuendo, however, as Curtis has said, "Common sense calmly replies that no legitimate work in any calling can go on effectively in the presence of unbidden and ill-informed persons, suspicious if not hostile."

The appointment of persons whose qualifications to inspect laboratories are not stated is unjustifiable. To inspect banks experts in banking are appointed; to inspect laboratories experts in experimentation should be specified. The grossest errors of judgment have been made by ignorant persons, incapable, for example, of distinguishing between reflex movements of brainless animals and purposive acts. But the petitioners for restrictive legislation will not admit that experts in experimentation are fit persons to trust.

Even when inspectors are competent, as British experience has shown, they either become suspected of being in league with the experimenters, because they so rarely report abuses, or they are said not to be present in the laboratories when the atrocities are being perpetrated. Not content with occasional inspection, therefore, the British antivivisectionists are now advocating constant attendance of inspectors in laboratories so that nothing may escape scrutiny. The absurdity of this scheme is its strongest condemnation. Evidently no amount of inspection is going to satisfy the agitators unless their pre-conceptions are to be substantiated.

Besides the foregoing special objections to bills which are hostile to operations on animals, there are certain general objections:

1. *Restrictive legislation is not needed.* The welfare of the animals used in experimentation is already safeguarded by voluntarily imposed regulations providing for their bodily comfort, for their use in important purposes, and for their freedom from pain. The regulations, drawn up by the Bureau for the Protection of Medical Research of the American Medical Association, have been adopted by corporate vote in practically every medical school in the country in which research is being conducted. Mr. Henry Bergh, of the American Society for the Prevention of Cruelty to Animals, has referred to these as "the most exemplary, humane and beneficent regulations governing the practice of vivisection to meet the requirements of humanity." Only the director of the laboratory can make exceptions to the rules and he can do so only in the rare case in which anesthesia or death of the animal would defeat the object of the experiments.³

The general adoption of the regulations in schools with active laboratories renders further legislation unnecessary. Burdening the statute books with unnecessary legislation is admittedly reprehensible.

2. *Such restrictive legislation is indefensible class legislation.* It is the function of the state to enact general laws against cruelty to animals; the proposed legislation places scientific men under peculiar surveillance and limitation. This is unwarrantable. The general laws regarding cruelty are adequate to cover cases of wanton infliction of pain, no matter by whom inflicted. A few years ago a professor in a veterinary school was convicted of cruelty on this basis, whether justly or not is not now pertinent; the fact is that the existing general law was adequate. Similarly two students of "optometry," in New York, were convicted under the general law providing for the punishment of causing in animals "unjustifiable physical pain, suffering or death." It is proper, therefore, to demand that the general laws against cruelty be applied before special legislation is framed.

3. See Cannon, W. B.: *Medical Control of Vivisection, Defense of Research Pamphlet*, xvi. 1910.

3. Such restrictive legislation is merely initial—an entering wedge—advocated with the purpose of advocating later more stringent law. In the *Journal of Zoophily* (March, 1909) is this statement:

We believe that in the course of time we shall have total abolition of vivisection, but as we cannot get it now, we think we may be justified in asking for something that will help the poor animals a little. Though we may not get abolition at once, we shall eventually.

This is the attitude taken by the moving spirits among the opponents of animal experimentation everywhere. As already shown, Great Britain has had a restrictive law, with registration of buildings, reports of experiments, and inspection, for thirty-six years. Yet there is no country in which agitation for abolition of animal experimentation is more active. The passage of the proposed legislation would therefore not allay agitation.

No other civilized country has followed Great Britain's lead; no British dependency has done as the mother country has done. As Sir Michael Foster declared, with reference to the British Act, "England offers in this respect at least an example to be shunned alike by her offspring and by her fellows."

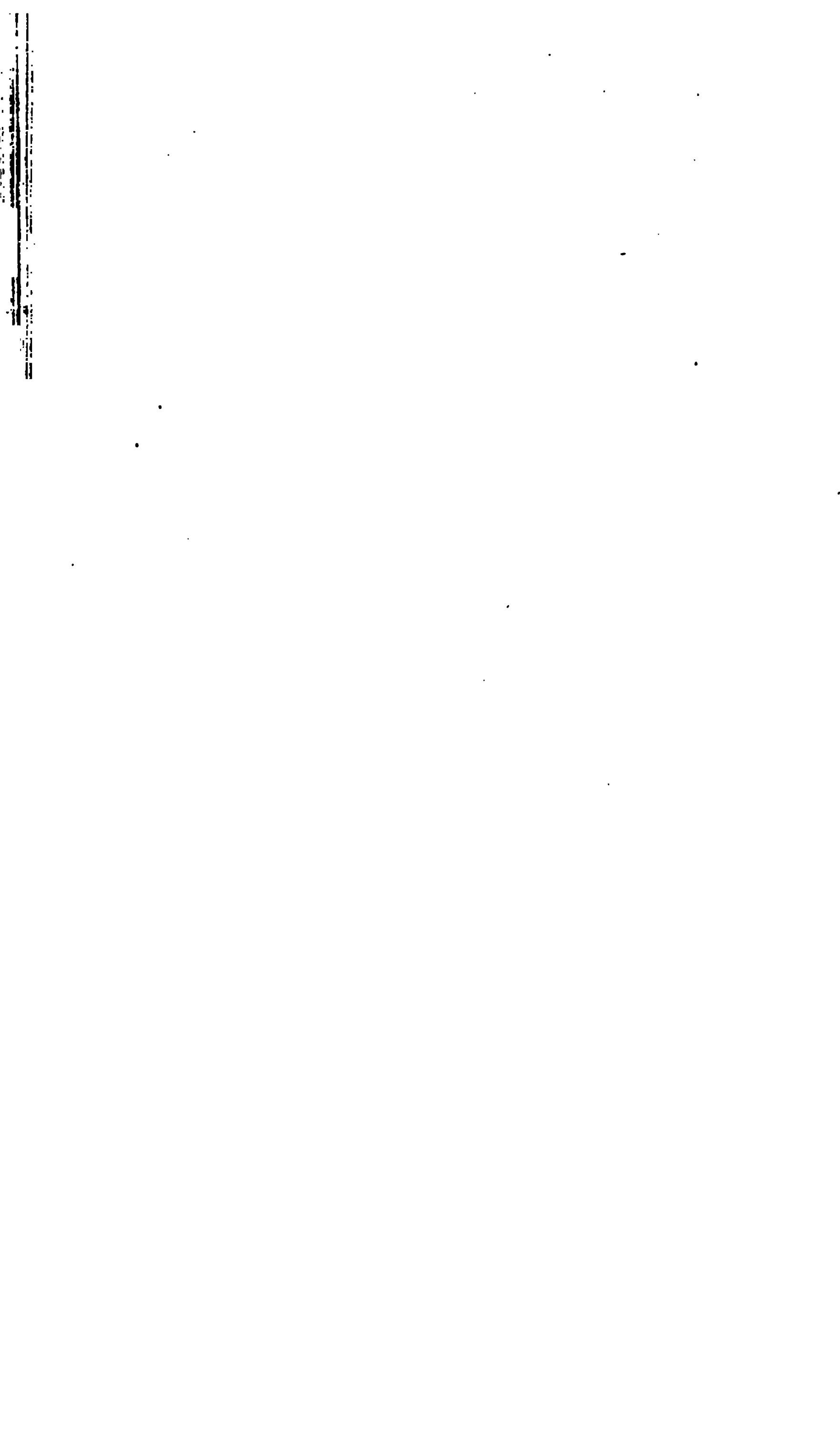
In conclusion I wish to urge that everything possible be done to enlighten the intelligent public as to the great practical results of animal experimentation, the important problems that remain to be solved, the ideals of the investigators who are trying to solve these problems, and the essential humanity of their methods. The pamphlets published by the Bureau for the Protection of Medical Research of the American Medical Association, and the leaflets issued by the Committee on Experimental Medicine of the New York State Medical Society present an overwhelming array of facts highly serviceable in such education. Physicians who use in daily practice the results of laboratory investigations can do nothing more useful to medical progress than combating antivivisection arguments and explaining the dangers of compromise.

And I also wish to urge further that sharp watch be kept on attempts to secure legislation that now or in the future would hamper, or in any way interfere with, the efforts of men engaged in medical research. Our opponents will try to get a foothold in one state or another;

and when they have done so they will point to that accomplishment as the result of their own prowess and as evidence of humanity and enlightenment of the people. And on the basis of action in one state they will begin work in others. For the welfare of mankind we must not permit their views to prevail.

Welch has summed up very precisely the reasons for opposing the efforts of the antivivisectionists. "The fundamental objection," he declared, "to the various legislative proposals to regulate animal experimentation by a system of licenses, of inspections, of specifications as to the purposes and conduct of the experiments, is that the enactment of such statutes would take the control of a matter of the highest importance to human welfare, and one requiring special knowledge and training and skill, out of the hands of the experts, who possess these qualifications, and would place it in charge of those who have not the requisite technical knowledge and experience. Not those who know, but those who do not know, would be given a discretion which might prove disastrous to the future of scientific medicine. This is a monstrously wrong principle to embody in legislation. Science has waged a long warfare through the centuries for freedom of investigation. The last of its battles is being waged to-day for freedom of experimental research in medicine. While I do not doubt the issue of this battle, I conceive it to be the duty of the public and of the press to support the cause of freedom in this contest, which is likewise that of true humanity."

Further information regarding antivivisection agitation, and regarding the value of animal experimentation to mankind, can be obtained by addressing the Bureau for the Protection of Medical Research of the American Medical Association, 535 Dearborn Avenue, Chicago, or the Committee on Experimental Medicine, New York State Medical Society, 17 West Forty-Third Street, New York City.



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The Charge of "Human Vivisection"
as Presented in Antivivisection
Literature

RICHARD M. PEARCE, M.D.
PHILADELPHIA

DEFENSE OF RESEARCH
PAMPHLET XXVI

Issued by the Bureau on Protection of Medical Research
of the Council on Health and Public Instruction of
the American Medical Association

"The humanity which would prevent human suffering is a deeper
and truer humanity than the humanity which would save pain or
death to animals."—Charles W. Eliot.

CHICAGO
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET
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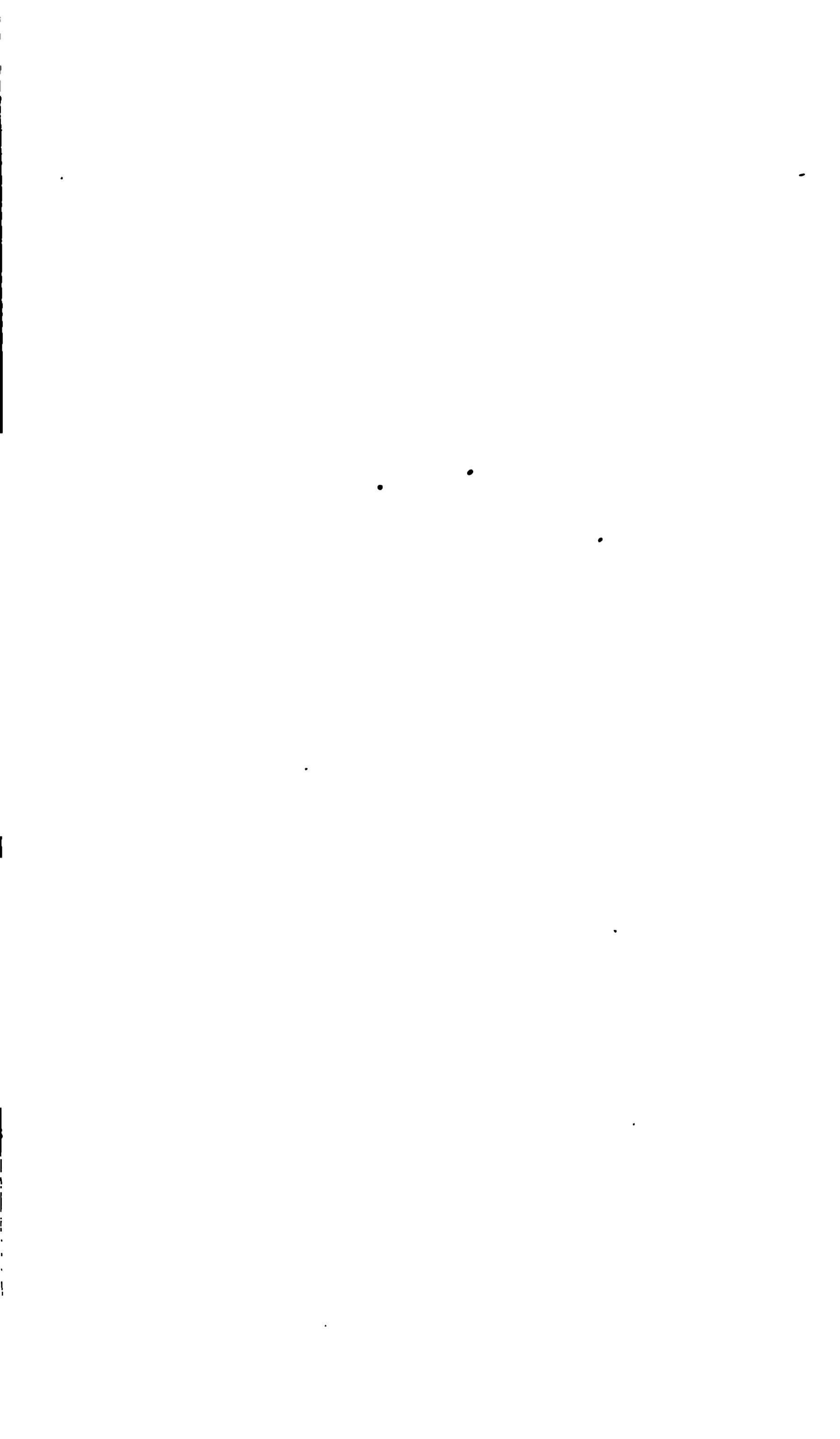
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The Charge of "Human Vivisection" as Presented in Antivivisection Literature

**RICHARD M. PEARCE, M.D.
PHILADELPHIA**



THE CHARGE OF "HUMAN VIVISECTION" AS PRESENTED IN ANTIVIVI- SECTION LITERATURE *

RICHARD M. PEARCE, M.D.
PHILADELPHIA

In the literature distributed by the American Antivivisection Society at its exhibit held in Philadelphia in the winter of 1913-1914 are many statements of great interest to all who are working for improvements in public health matters, and of vital importance to every member of a profession which has for its ideal the relief or abolition of suffering caused by disease. In brief, this literature indicates that the recent activities of the antivivisectionists are directed not so much against animal experimentation as against the adoption of new methods of scientific procedures in the practice of medicine.

This is evident in (1) the misrepresentation of the medical profession in connection with procedures which the antivivisectionists term "human vivisection," and (2) the apparent cooperation of the American Antivivisection Society with forces opposed to the improvement of the public health.

I. MISREPRESENTATIONS AS TO "HUMAN VIVISECTION"

In presenting the evidence bearing on the first of these two points I shall utilize only the literature bearing the stamp of the American Antivivisection Society, the New York Antivivisection Society, the British Union for the Abolition of Vivisection (the British antivivisection society) or the Vivisection Investigation League of New York.

* Presented at the Tenth Annual Conference on Public Health and Education and reprinted as Pamphlet No. 26 of the Protection of Medical Research series, issued by the Council on Health and Public Instruction of the American Medical Association. Copies can be secured for 10 cents each. This series consists of twenty-six pamphlets, taking up the relations of animal experimentation to ethics, diagnosis, cancer, vaccination, the live stock industry, tuberculosis, typhoid, dysentery, plague, rabies, surgery, internal secretions, the circulation of the blood, protozoan tropical diseases, etc.

Not all the statements presented in these pamphlets can be traced to their sources, for many of them consist of quotations from the daily papers or from the *Journal of Zoophily* and the *Abolitionist*, and frequently even those quoted from medical journals are given without original sources or are based on a summary of the literature or on some other equally indirect account. As these cannot readily be verified and as Dr. Keen¹ has previously covered the references to foreign literature, I have limited my investigation to references to original papers in American medical publications.

FIVE ANTIVIVISECTIONIST QUESTIONS

In a pamphlet entitled "Human Vivisection" (bearing the name of the New York Antivivisection Society), five questions are asked:

1. Would you like to have your body inoculated with consumption germs?

In connection with this question is given a newspaper account (*New York Herald*) of a paper read by Professor Detre of the University of Budapest at the International Tuberculosis Congress in Washington in 1908. The pamphlet states that "he had inoculated nine children in Hungary with a serum he had discovered. He urged further demonstration in the interest of science. In consequence nine charity children suffering from incipient tuberculosis in the Children's Hospital at Washington were selected and germs of both bovine and human tuberculosis were injected."

I have investigated this account through Dr. John F. Anderson of Washington, D. C., director of the Hygienic Laboratory of the United States Public Health Service. From Dr. Anderson's account it is seen that in the first place Detre² did not use a serum, and in the second place did not inject the germs of tuberculosis. What he really did was to scratch the skin as in vaccination and apply by von Pirquet's method "old tuberculin," that is, a heated fluid in which tubercle bacilli had been grown, but which is entirely freed from such bacilli.

1. Keen, W. W.: Misstatements on Antivivisection, THE JOURNAL A. M. A., Feb. 23, 1901, p. 500; Misstatements of the Antivivisectionists Again, THE JOURNAL A. M. A., Aug. 10, 1901, p. 400.

2. See Detre's original account, Proc. Sixth Internat. Cong. Tuberc., Section I, Vol. I, Part I, p. 515.

Dr. Anderson's statement follows:

Detre's experiments at the Children's Hospital were for the purpose of demonstrating the truth of the claim by him that he could differentiate, by means of a von Pirquet reaction, between infection with bovine and human tuberculosis. The children were not actually inoculated, but the experiments were simply a simultaneous von Pirquet, using at different points old tuberculin made from the human strain and from the bovine strain. . . . The children certainly suffered no ill effects therefrom.

The other reference under this first question is to an investigation in Philadelphia in which tuberculin was used as a diagnostic measure. A sentence runs, "More than half the cases *reacted* (which means they were infected with tuberculosis in a modified form) and some suffered very serious complications. . . ." To the medical man the fact that these individuals "reacted"³ means that they were suffering from tuberculosis before the use of tuberculin; but to the layman the implication is that the use of tuberculin brought about *de novo* an infection with "tuberculosis in a modified form." It is not stated that in the preparation of tuberculin all tubercle bacilli are destroyed and that therefore it cannot cause tuberculosis; on the contrary, the impression given is that living bacteria were used.⁴

2. A second question is: Would you like to have your daughter given the most awful and vile disease known? In their answer to this question nothing is presented which bears on medical practice in America.

3. Would you like your son to be inoculated with scarlet fever or poisonous pus? The reference here is to Dr. J. W. Stickler of Orange, N. J., who is charged with inoculating a little girl of 4 and a boy of 8 years with foot-and-mouth disease and with exposing these children after recovery from foot-and-mouth disease to the infection of scarlet fever. I have examined Dr.

3. The word "reacted" as used in medical practice indicates that the result of the test was positive and showed that the individual was suffering from tuberculosis. Thus, when tuberculin is scratched into the skin (von Pirquet method) or dropped on the surface of the eye (Calmette method) a local reddening occurs. This local reaction does not mean that tuberculosis is produced locally, but merely that tuberculosis is present somewhere in the body. In the absence of tuberculosis no "reaction" occurs.

4. For a more complete account of these misrepresentations, see the discussion of tuberculin, later.

Stickler's original report⁵ and find that the statement of fact is correct. Dr. Stickler shortly afterward committed suicide and the evidence in the case and the opinions of his most intimate friends are that he was of unsound mind at the time he made these experiments.†

4. Would you like to have cancer grafted into your well breast so that it took root there? In their answer to this question, as in the second, no American literature is cited.

5. Would you, a decent woman, after the anguish of childbirth, like to be inoculated by the hospital doctor with loathsome disease, and put with the degraded women suffering these diseases? This question, again, is not supported by reference to American literature. It is, however, as are also the second and fourth questions, put in such a way by an American society as to suggest that the procedures indicated are constant occurrences in American hospitals.

In connection with the second, fourth and fifth questions, no support of the implications is offered, and the data presented in connection with the first question, concerning inoculation with tubercle bacilli, has no basis in fact. In connection with the third only is there an adequate basis in American medical literature, and even in this the question gives a false impression, for the children were exposed to, not inoculated with, scarlet fever. They were, however, subjected to inoculation with material from the vesicles of foot-and-mouth disease. From Dr. Stickler's description it is not clear that he reproduced the disease. Nevertheless it is difficult to excuse such procedures. As the result of his clinical experience Dr. Stickler believed that foot-and-

5. Stickler: Med. Rec., New York, Dec. 10, 1887.

† Dr. W. P. Northrup writes to me as follows: I was a personal friend of "Joe" Stickler and recall that he brought to me his experiments with foot and mouth disease as a prophylactic against scarlet fever for the purpose of obtaining from me patients on whom to try the measure. The proposition was turned down. It was taken to others, and among them Dr. Abraham Jacobi, by whom the proposition was turned down in such emphatic terms that nothing more was heard of it. I remember that Dr. Stickler injected himself with the disease and was very sick with alarming symptoms for a few days. He committed suicide. Among his papers was found one requesting his wife to publish his experiments after his death. His suicide completed the impression that he was mentally unbalanced for a time—"obsessed" with the idea that he was immortalizing his name and would deserve the gratitude of future generations. I was a personal friend, and roomed with him as a medical student, and visited him at his home. I regret bringing this unhappy incident to light again and would shield my friend's memory, but under the present circumstances it seems right to publish these facts. My friend was apparently "obsessed" with the delusion that he had made a "great discovery."

mouth disease protected against scarlet fever, and in an attempt to prove this he made the experiments described. In this his procedure was not different from that of Jenner in connection with cow-pox and small-pox. But our knowledge of the infectious diseases in 1887 justified methods other than those of Jenner. I doubt whether to-day such observations as those of Stickler would receive the support of any reputable physician. Certainly these isolated observations of twenty-seven years ago cannot be taken as a criterion of what would be done to-day in the light of our wider knowledge.

THE ATROPIN-MORPHIN INVESTIGATION

Aside from the matter covered by these five questions, the pamphlet gives three other descriptions of so-called "human vivisection" in this country. One is of observations in a "United States Army Hospital" on the antagonistic action of atropin and morphin. These, it is stated, were made on soldiers, and the criminal character of the procedure lies apparently in the fact, as quoted from the original, that "in no instance were they allowed to know what agents were used, or what effects were expected." The investigation in question is that of Drs. S. Weir Mitchell, William W. Keen and George R. Morehouse,⁶ which had for its object the relief of pain in "those terrible cases of neuralgia which, in some shape, are apt to follow as a consequence of neural injuries." These nerve-injuries, it must be understood, were those following gunshot and other wounds of warfare. After trying many drugs it was found that morphin alone in many instances seemed able "to overcome the anguish of certain forms of neuralgic distress." But, although morphin gave relief from the "agony" and "anguish" of these nerve-wounds, it had certain inconveniences, and these, in view of the necessity of administering to some patients as many as from twenty to thirty hypodermic injections a day, became a serious matter. It was in an attempt to overcome them that the investigation of the effect of a combination of atropin and morphin was undertaken. As a result of these investigations the use of atropin with morphin has become a commonplace of

6. Mitchell, S. Weir; Keen, W. W., and Morehouse, George R.: On the Antagonism of Atropia and Morphia, Founded on Observations and Experiments made at the United States Army Hospital for Injuries and Diseases of the Nervous System. Am. Jour. Med. Sc., 1865. L, 67.

therapeutic procedure, and standard tablets containing these drugs are used all over the world with little thought of the clinical difficulties which led Mitchell, Keen and Morehouse to make their original study. As to the charge of experimentation without the knowledge of the patient, Dr. Keen⁷ has elsewhere made the following statement:

Most of our patients operated on (entirely by hypodermic injections) were sorely in need of relief. A few were convalescents. In all cases we avoided telling them what drug was being used, for every one knows how imagination, fear or other emotion would alter the rate of the pulse or of the breathing. Not one man was injured in the least. Not one ever complained.

This investigation constitutes one of the most important pharmacologic and therapeutic contributions in American medical literature. Many thousands of human beings have been benefited and many lives saved through the knowledge thus obtained, but to the opponents of medical investigation it is merely an example of "human vivisection."

OBSERVATIONS OF THYROID EXTRACT IN THE INSANE

Another quotation concerns Dr. Henry J. Berkley of Johns Hopkins Hospital and his observations concerning the effect of preparations of the thyroid gland on insane patients. He is quoted as saying in regard to the thyroid preparation that "when its administration is pushed even to a moderate degree it almost invariably results in death," and that "two patients became frenzied and of these one died before the excitement had subsided." In the opening paragraph of his paper Berkley⁸ reviews the current views concerning the clinical use of thyroid extract, and it is in the second paragraph, where he refers to both man and animals, that one of the foregoing quotations occurs, that is, that "when this administration is pushed even to a moderate degree death is almost invariably the result." This is a general statement based on the literature which has accumulated in connection with the use of thyroid extracts and covers not only clinical but also experimental work on animals. It is not, as is implied in

7. Keen, W. W.: The Influence of Vivisection on Character, A.M.A. Defense of Research Pamphlet XXIV, 1912.

8. Berkley, Henry J.: Studies on the Lesions Induced by the Action of Certain Poisons on the Cortical Nerve-Cells. VII. Poisoning with Preparations of the Thyroid Gland, Bull. Johns Hopkins Hosp., July, 1897.

the antivivisection pamphlet, a conclusion based on Dr. Berkley's work.

In connection with the second statement, "Two patients became frenzied, and of these one died before the excitement subsided," the pamphlet does not give the rest of the sentence, "the immediate cause of the exitus being an acute disseminated tuberculosis"; nor does it state that the death occurred seven weeks after thyroid treatment had been discontinued. Furthermore, it does not state that the frenzy may have been a manifestation of mental derangement and not of the action of the thyroid preparation.

Both of these quotations are excellent examples of the way the opponents of medical research misrepresent medical literature. It is true that Dr. Berkley's treatment was carried out on insane patients, but he definitely states that the initial treatment was 5 grains daily for three days, then after a certain tolerance had been established 10 grains, and unless the symptoms induced became grave, the dose was increased to 15 grains daily. There is every evidence that in order to obtain information concerning the value of this treatment, as well as its dangers, he used every precaution possible. That many of the patients improved and that two were sent home on this account is not stated by those who quote him. That Dr. Berkley should point out that the treatment may have its dangers does not make it human vivisection. Thyroid gland has been and still is used in medical treatment—and the doses used to-day are as large as or even larger than those administered by Dr. Berkley. Moreover, it may be pointed out that Dr. W. W. Keen called attention to these errors of statement in 1901, as did also Dr. W. B. Cannon in 1911. They have, however, never been corrected. Indeed, this ancient slander of Dr. Berkley has, without the slightest regard for truthful statement or sense of fair play, been repeated within the last few months. It is this disregard of all sense of fairness and decency in connection with the use of Dr. Berkley's report that has opened the eyes of many fair-minded persons to the fact that antivivisection literature is largely a literature of falsehood and misrepresentation.

Only three other American references are given in this pamphlet. One of these, referring to lumbar puncture, I shall discuss later. Of the other two, one is a proposition by the vice-president of a state board of

health that the state board of pardons grant the privilege of inoculating convicted criminals with the germs of tuberculosis, and the other tells of a paper read by a physician in Illinois in which the suggestion was made that criminals condemned to capital punishment be turned over to the experimental physiologist.

Neither of these statements need be taken seriously; but even if they do represent the opinion of a few physicians, they differ in no way from the suggestion of one of our local antivivisection leaders (Caroline Earle White), who suggests that in India the persons condemned to death as the result of snake-bite be used for experimental purposes. "Here is an opportunity," writes Mrs. White, "such as is not often offered for experimenting upon human beings, since as they would invariably die from the snake bite, there can be no objection to trying upon them every variety of antidote that can be discovered." After all, this suggestion by an antivivisectionist is not very different from the two concerning criminals.

MISREPRESENTATION OF LUMBAR PUNCTURE

Much attention is given by the antivivisection societies at present to lumbar puncture and the serum treatment of meningitis as forms of "human vivisection." This term is one which is very appropriate for any surgical operation on man, but it is difficult to understand how it can be applied to the various diagnostic procedures or curative inoculations, which have developed recently, from which modern medicine has derived so many benefits and on which it bases its hope of future control of the infectious diseases. In the exhibit of the American Antivivisection Society is a picture⁹ showing a nurse and (presumably) a physician standing one on each side of a table on which a child lies. The physician is apparently about to perform the simple procedure known as lumbar puncture, that is, to remove for purposes of diagnosis and treatment a small amount of fluid from the spinal canal. Of the fact that this is the present-day routine procedure in all cases of evident or suspected meningitis, no mention is made. That on lumbar puncture depends both the diagnosis and the treatment of meningitis is not even suggested. Thus a humane and life-saving procedure is presented to the

9. The pamphlet reproducing this picture is labeled "Human Material for Scientific Research," and below the picture are the words "Human Vivisection."

thoughtless public as a form of so-called human vivisection.

In the pamphlet of the New York society, previously mentioned, is the oft-quoted statement that "Dr. A. H. Wentworth, Senior Assistant Physician to The Infants' Hospital, Boston, made forty-five vivisections tapping the spinal canals of children, many of whom died." It has been pointed out time and time again that forty-five punctures were made in twenty-seven living and three dead children, and that of the twenty-seven, fourteen died, not at the time or as the result of the puncture, but, as the necropsies showed, and as is stated in Wentworth's paper, from which the New York Society quotes, of definite morbid processes. Dr. W. W. Keen and Dr. W. B. Cannon have called the attention of the antivivisectionists to their unjust and misleading statements concerning these cases, and although one of the members of the American Antivivisection Society has acknowledged that she "unconsciously exaggerated"—she had stated that "every one" of the children died—the story is still preserved in a form which magnifies the number of children and gives the impression that lumbar puncture was the cause of death. And this is done despite the fact that lumbar puncture is now accepted as one of the most important procedures in the diagnosis of acute and chronic cerebrospinal diseases, is essential in the treatment of epidemic cerebrospinal meningitis, is a constant procedure in surgery when spinal anesthesia is desired, and is frequently employed as a method of diagnosis when traumatic injuries of the spine exist.

MISLEADING STATEMENTS AS TO SERUM TREATMENT OF MENINGITIS

In connection with the serum treatment of meningitis a most misleading pamphlet is put out by the American Antivivisection Society. It contains the following:

We are indebted to the Vivisection Investigation League of New York for the following refutation of Dr. Flexner's claims:

Dr. Flexner of the Rockefeller Institute says of cerebrospinal meningitis that "where 75 per cent. died, now 75 per cent. recover." The New York City Health Department, in its weekly report, says that there were in Greater New York:

	Cases	Deaths	Case Fatalities Per Cent.
1905	2,670	2,025	75.8
1906	980	813	82.9
1907	795	652	82.1
1908	396	359	90.6
1909	339	330	97.3

In Greater New York, 24 deaths, January, 1910. The last annual report, 1908, of the New York City Health Department says that "the endemic level as it was previous to the outbreak of 1904 has at last been reached, the death-rate per 1,000 being 0.07 during 1908, which is exactly the same as the death-rate from 1900 to 1903. . . . The disease was apparently more fatal during 1908 than the year before. . . . *The antimeningitis serum was first used in April, 1907.*" [Italics in pamphlet.]

This statement and table give the impression that all the cases included since 1906 in the New York report were cases of epidemic meningitis, and that in all the Flexner serum was used. As a matter of fact the serum was not in general use; but on account of the small amounts prepared in the early period of its clinical application, it was distributed to physicians only on request. Of the cases listed by the health department a comparatively small number received this specific treatment. It is very evident, therefore, that no opinion concerning the efficacy of the serum can be based on the figures of the health department. The average mortality for the 2,510 cases in 1906-1909 as given by the health department is 88.2 per cent.; but in the report (1909) of the first collection of 712 cases¹⁰ actually treated with serum after bacteriologic examination, the mortality was only 31.4 per cent., and in the recent report of 1,294 cases¹¹ occurring in all parts of the world, the mortality after serum treatment was 30.9 per cent. Moreover, it was shown that when the serum was given on the first to the third days, the mortality was only 18.1 per cent. The value of the specific serum can be discussed fairly only in the light of the later figures. The absurdity of the Vivisection Investigating League's method of juggling statistics is so self-evident that one wonders it should be attempted. It would be as fair to base the mortality following the surgical

10. Flexner, Simon: The Present Status of the Serum Therapy of Epidemic Cerebrospinal Meningitis, THE JOURNAL A. M. A., Oct. 30, 1909, p. 1443.

11. Flexner, Simon: The Results of the Serum Treatment in Thirteen Hundred Cases of Epidemic Meningitis, Jour. Exper. Med., 1913, xvii, 553.

treatment of appendicitis on the total deaths from appendicitis.

Many other statements are also misleading, as that which states that meningitis "cannot be contagious, as it is merely a possible complication of other diseases." That certain forms of meningitis are complications of other diseases is of course true, but by making the statement the pamphlet implies that epidemic meningitis due to a specific cause does not exist. But more misleading, in view of the remarks on the lack of efficacy of the serum, are the following:

At this time of year there prevail in many parts of Europe, as of America, epidemics of eruptive fevers such as measles, scarlet fever, influenza, etc., all of a light form.

There were, therefore, selected from among these cases for experimental purposes those which, as they presented certain meningeal disturbances as well as the usual symptoms of measles or of scarlet fever, seemed to justify the title of cerebrospinal meningitis, and they were then inoculated.

To those who have used the serum the falsity of these statements is at once evident when it is recalled that the serum is used only when the meningococcus is found by lumbar puncture, and that when other organisms are found the serum is not used. In this connection may be presented the statement of Dr. Dunn¹² of the Children's Hospital, Boston:

My personal experience may be cited to illustrate the value, up to this time, of the general health reports on meningitis. Outside my regular hospital services, I have been called on to administer the antimeningitis serum in 142 consecutive cases of meningitis which were believed by the attending physicians to be examples of the epidemic disease. On performing lumbar puncture and making bacteriologic examinations, I found that only sixty were cases of epidemic meningitis, while sixty more were cases of tuberculosis, twelve of pneumococcus, six of streptococcus and four of influenzal meningitis. Among the sixty cases of epidemic meningitis in which I administered the serum, there were forty-five recoveries, equaling 75 per cent., while of the eighty-two miscellaneous cases all patients died but one. This experience is by no means unique, but is rather the rule. It is quite certain that all these cases would, under ordinary conditions, have been reported, assuming meningitis to be a generally notifiable disease, as epidemic meningitis; and under these

12. Dunn, Charles Hunter: Animal Experimentation in Relation to Epidemic Cerebrospinal Meningitis, A. M. A. Defense of Research pamphlet XXI.

STUDY OF 180 CASES OF MENINGITIS

Clinical Diagnoses Reported by Attending Physician	Final Diagnosis Established by Combined Clinical and Laboratory Examination
Epidemic meningitis, 71 cases	Epidemic meningitis 27 Tuberculous meningitis..... 17 Ac. suppurative meningitis due to: Pneumococcus 4 Streptococcus 7 Streptococcus mucosus capsulatus..... 1 Influenza 1 Unidentified Gram coccus (no growth) 1 Enteritis 1 Bronchopneumonia 2 Cerebral endarteritis 1 Intestinal intoxication 2 Delirium tremens 1 Gastro-intestinal acidosis... 1 Measles 1 Simple chro. internal hydrocephalus 1 No meningitis (undetermined diagnosis) 20
Meningitis unclassified, 74 cases	Epidemic meningitis 8 Tuberculous meningitis..... 10 Poliomyelitis or poliencaphalitis 13 Enteritis 3 Bronchopneumonia 11 Lobar pneumonia 4 Hysteria 2 Purpura hemorrhagica..... 1 Intestinal intoxication 2 Cerebrospinal lues 1 Fractured skull 1 Spastic paraplegia 1
Tuberculous meningitis, 28 cases	Tuberculous meningitis 23 Epidemic meningitis 1 Streptococcus meningitis .. 2 Undetermined diagnosis, but no tuberculous meningitis 2
Poliomyelitis or poliencaphalitis, 7 cases	Poliomyelitis or poliencaphalitis 6 Epidemic meningitis 1

circumstances and in spite of the serum treatment, the records would have shown a mortality of 67.6 per cent. Instead of this the mortality from all the forms together, except the epidemic, should properly have been given at approximately 100 per cent., and of the epidemic disease at 25 per cent.

Other evidence of the same nature is at hand as the result of a special investigation by the New York City Department of Health. July 1, 1910, Drs. Sophian,

DuBois and Neal¹³ undertook under Dr. Park's direction in the laboratory of the city department of health the study and treatment of meningitis in connection with the preparation and standardization of antimeningitis serum. They were notified whenever a case was reported and communicated at once with the physician in charge, usually making an appointment with him to see the case. The accompanying table shows the result of their study of 180 cases.

Of the first group clinically considered as epidemic meningitis, only about a third, and of the second group, classified broadly as meningitis, only one-ninth could have received the slightest benefit from the specific serum. In the third and fourth groups the serum obviously would not be used. Still it is on the death-rate in the total number of cases thus variously reported that, without regard to the question of exact diagnosis and with absolute disregard of whether or not the specific serum was used, the antivivisectionists would base their claim that this serum is of no value.

Again, in contrast with the New York Society's point of view, is that of Dr. Thomas Morgan Rotch¹⁴ of the Children's Hospital, Boston. During eight years Dr. Rotch had treated meningitis in various ways with a mortality varying from 60 to 80 per cent.; but in the first year (Nov. 1, 1907 to Nov. 1, 1908) after he began the use of the Flexner serum he treated 74 cases, with a decrease in mortality from 80 to 19 per cent.

In view of such results the average person of humane instincts wonders whether the money of the Vivisection Investigating League of New York might not be better spent in educating the public concerning the life-saving power of such treatment—and indeed in financing the manufacture and distribution of this serum so that it could be used by every physician in the earliest stages of epidemic meningitis.

CRITICISMS OF THE USE OF TUBERCULIN

Another pamphlet of the New York Antivivisection Society with the heading "Vivisectors Clamor for Human Beings to Vivisect" refers to the work of Dr. L. Emmett Holt, at the Babies' Hospital, New York.

13. Sophian. DuBois and Neal: Studies on Meningitis during 1911, Collected Studies from the Research Laboratory, Department of Health, City of New York, 1911. vi. 15.

14. Rotch. Thomas Morgan: Abstract of Discussion on article by Flexner, THE JOURNAL A. M. A., Oct. 30, 1909, p. 1444.

Sentences are quoted of Holt's study of the various methods of applying the tuberculin test in the diagnosis of tuberculosis. It is difficult to see how these valuable and constantly used clinical tests can be used to support the claim of human vivisection. Only by misrepresentation and by misinterpretation can they be so used. Let me quote from the pamphlet two paragraphs, referring to Dr. Holt's work.

The ophthalmic test was made 615 times; the skin test of von Pirquet was employed 217 times, also on non-tuberculous and dying babies. As though this useless and cruel torture of ailing children was not sufficient, the puncture reaction was practiced on 130 cases, the result of which was to produce a high fever.

Altogether there were over 1,000 tests made on hundreds of little, helpless children, who may suffer from these injections during their entire lives, yet Dr. Holt is forced to this humiliating admission: "It will be seen that some failures and some unexplained reactions occurred with all of the tests. The results with any test cannot, therefore, be regarded as conclusive."

By writing into the text what they wish to prove they imply that these tests are fraught with danger and that the results of such clinical studies are of no value.

An examination of Dr. Holt's paper¹⁵ shows that he does say that "the results with any test cannot, therefore, be regarded as conclusive," but the rest of the sentence, not quoted in the antivivisectionist pamphlet goes on "though a positive reaction creates a very strong possibility that tuberculosis is present. This is increased if the result is confirmed by other tests." In another place Holt says, "While of the greatest assistance in diagnosis, the various tests are always to be taken in connection with the general symptom and the physical signs," and again, "Routine tests proved of considerable value in revealing cases of tuberculosis not hitherto suspected." Referring to the eye test, Dr. Holt says, ". . . in no case was the test followed by any unpleasant results."

Another paper on the use of tuberculin, that by Drs. Hamill, Carpenter and Cope,¹⁶ has likewise been used

15. Holt, L. Emmett: A Report on One Thousand Tuberculin Tests in Young Children, Arch. Pediat., 1909, xxvi, 1.

16. Hamill, S. M.: Carpenter, H. C., and Cope, T. A.: A Comparison of the von Pirquet, Calmette and Moro Tuberculin Tests and Their Diagnostic Value, Arch. Int. Med., December, 1908, p. 405.

freely by the various antivivisection societies. References to it appear in three of the pamphlets of the American and in two of the New York Antivivisection Society. In two of the pamphlets of the former society colored pictures of the eye showing the reaction are presented. Two of these pamphlets have the title "Human Vivisection," the third, "Vivisectors Clamor for Human Beings to Vivisect," the fourth, "Tuberculin Tests on Human Beings," and the fifth has the full title of the paper by Hamill, Carpenter and Cope. In one pamphlet occurs the subheading "Experiments on Babies and Little Children" and in another, "Some Recent Instances of this Deadly Work on a Large Scale Follows."

As so much attention has been given by the antivivisectionists to the tuberculin reaction, I wish to go into detail concerning the observations of Hamill and his associates, and for the benefit of non-medical readers to explain the diagnostic procedure known as the tuberculin test. This depends on the principle that if a fluid in which tubercle bacilli have grown, and which therefore contains the chemical products of their growth, is injected into an animal or person suffering from tuberculosis, a transient increase of temperature occurs and constitutes the chief sign of a positive reaction; if no tuberculosis exists, no reaction occurs. The method is therefore of great value as a diagnostic test in obscure or doubtful cases of tuberculosis. Not only is it used in recognizing tuberculosis in man, but it is the constantly and generally recognized procedure in determining the presence of tuberculosis in cattle.

The fluid injected is called tuberculin, and as it is sterilized it contains no living bacteria and cannot cause tuberculosis. When the test was first used, the tuberculin was injected beneath the skin with the aid of a hypodermic syringe, and the chief reaction which this method gives, is, as I have stated, an increase in temperature. Later it was found that if the diluted tuberculin was placed on the surface of the eye, there followed in tuberculous persons a reddening or congestion of the eye, which might go on to the stage of mild conjunctivitis ("pink eye"). This is known as the Calmette reaction. Still later it was discovered that if the skin was scraped, as in vaccination against small-pox, and the tuberculin applied over such an area, a local

reddening—the von Pirquet reaction—could be obtained. There has never been any doubt about the value of the tuberculin reaction. It is one of the most valuable adjuvants in the diagnosis of doubtful tuberculosis. When, however, about six or seven years ago, the medical profession had its choice of three methods of applying the test, it was most important to find out which (1) gave the most constant results, (2) was the simplest to apply, and (3) was accompanied by the fewest disagreeable complications; to determine these points and to establish the best method of procedure was the object of several clinical investigators.¹⁷ The work of Dr. Hamill and his associates constituted one of the earliest of these investigations in this country. Now let us see how this work has been misrepresented. We find the statement “inoculations of tuberculin into children . . . many of the injections being made into the eye.” The word “injection” suggests the propulsion of a fluid through a syringe with sufficient force to cause it to enter a tissue or cavity. In the test under consideration the fluid is allowed to drop on the surface of the eye from the ordinary medicine- or eye-dropper. As used, the above-quoted phrase implies that the tuberculin was introduced *into* the substance of the eye and not, as has been explained, dropped on the surface of the eye or inner side of the eyelid.

Another statement is, “More than half the cases reacted (which means they were infected with tuberculosis in a modified form)” The words in parenthesis have no basis in fact. Tuberculin, in that it contains no living bacteria, cannot cause infection, and the reaction which it causes is not “tuberculosis in a modified form.” The presence of the reaction merely shows that in the individual tested tuberculosis exists. Lack of knowledge of the principles of bacteriology and immunity may have led the writer of the

17. Studies for this purpose, other than those of Holt and of Hamill, Carpenter and Cope, that have been quoted at length by the antivivisectionists are Hamman, L. and Wolman, S.: The Cutaneous and Conjunctival Tuberculin Tests in the Diagnosis of Pulmonary Tuberculosis, Arch. Int. Med., May, 1909, p. 307. Taussig, A. E.: The New Conjunctival Test for Tuberculosis, Interstate Med. Jour., 1908, 531. Fisch, C.: The Present Status of Ophthalmic Diagnosis of Tuberculosis, Interstate Med. Jour., 1908, 533. Many others are quoted more briefly. Practically all these point out the occasional danger of the eye-test and thus support the work of Hamill and his coworkers, who were among the first to sound a note of caution. In this way the antivivisectionist literature unconsciously offers a justification for Hamill's studies.

pamphlet to use this misleading phrase, but as the reaction is clearly explained in the original paper, it appears rather as a deliberate and malicious introduction of false matter. In these various pamphlets it is implied that the investigation was entered on recklessly and without thought of the consequences. In this connection a statement of Dr. Hamill¹⁸ is of interest:

Before undertaking the work, I went over the available literature and conferred with Dr. —— to see what information I could get concerning the tests. I knew that —— had applied the conjunctival test to some sixty cases, and I wanted to know whether he would advise against my undertaking the application of that test to the children in St. Vincent's Home. After warning me against applying it to inflamed eyes or in the cases of children with histories of previous eye trouble, he told me that he thought there was no reason why I should not proceed. I found nothing in the literature at that time that made me feel that there was any impropriety in undertaking the work.

This statement indicates that the investigation was not entered into hurriedly or without expert advice.

In some of these pamphlets it is implied that blindness resulted in some of the cases. For this there is no justification in the paper, for although the investigators state in describing the complications that these "*may* permanently affect the vision and even lead to its complete destruction," there is no evidence that the latter condition resulted. The statement quoted was made for the purpose of emphatically warning physicians against some of the dangers of the test. As a matter of fact, all the eyes cleared up except one in a patient in which a defect of vision of one eye persisted on account of a small corneal scar; in no instance did blindness result.

Although I have been unable to find in any of these pamphlets a statement that these investigations were made without the consent of those in charge of the home, some of the accounts refer to the children as "foundlings, orphans and destitute children," thus implying that they were used without authority. On this point the following statement of Dr. Hamill¹⁸ is of interest:

18. Personal letter.

I went with Dr. —— to Sister Marie, the Sister Superior of St. Vincent's Home, and we together explained to her that we wished to apply these tests for the double purpose of determining the incidence of tuberculosis among the cases in St. Vincent's Home and among those being admitted to the home, and at the same time to make a comparative study of the different tests. We were granted permission without any hesitation, and the work was conducted throughout my term of service without the slightest comment on the part of any one. But it was applied only to children in the home at that time. When I returned from my vacation in the autumn I prepared to apply the tests to children who were being admitted to the home, but gave this up after hearing from Dr. —— that there had been some criticism on the part of the Sisters of the work which had been done.

Again, in referring to an attack made on him by the *New York Herald*, Dr. Hamill continues:

An interesting sequel to the attack was that Dr. —— and I were called to the home some months after these publications appeared, to be introduced to the present Sister Superior, who told us that she had sent for me for the specific purpose of telling me how deeply she appreciated what I had done for the home; how intensely she regretted the experiences I had while connected with the home and to assure me that nothing would give her more gratification than to have me reinstated in the institution if opportunity arose. She informed me that she had carefully read the article which I had published, and had seen nothing in it to criticize.

In view of these criticisms of the use of tuberculin by Dr. Holt, Dr. Hamill and others, it is of interest to note that its value as a diagnostic test has been confirmed by federal, state and municipal health authorities, and that it has become one of the most important of modern procedures in medical diagnosis. As to the best method of application there is still some difference of opinion, but the "eye" test has a large group of supporters. Within the last few months Dr. J. Gutman¹⁹ of Brooklyn has stated that the test is safe, very reliable, and absolutely without danger, and serves the purpose as well as, if not better than, the skin reactions. He cautions against its use when any eye-trouble is present, but adds that he does not know of a single case in which the test has proved dangerous.

DISTORTED VIEW OF A CLINICAL TEST

The same pamphlet contains also an account of Noguchi's²⁰ clinical investigation of his luetin test for syphilis, which ends with the statement:

To the shame of the profession it must be added that physicians connected with twenty-two hospitals in New York City and vicinity contributed their patients to Noguchi for these merciless and unscrupulous experiments.

This base betrayal, on the part of hospital physicians, of a sacred trust would be impossible to any one other than the vivisector and his upholders.

Here again it is difficult to understand how a well-recognized clinical test which aids in the diagnosis of obscure cases of syphilis and which causes no reaction in the non-syphilitic can be used as an example of human vivisection.

Luetin is prepared from the micro-organism—*Spirochaeta pallida*—which causes syphilis. A suspension of this organism is so treated as to cause disintegration of the parasite. The material is then heated so as to ensure the death of all living material in the fluid. Phenol (carbolic acid) is added to prevent contamination, and the fluid—a sterile mixture—is injected into the skin, much in the manner employed in the tuberculin test. It is entirely devoid of living micro-organisms, as was shown by Noguchi, first on rabbits and monkeys, and later by applying it to his own skin and the skin of several physicians who volunteered for that purpose. The reaction in the syphilitic is a slight erythema (or reddening) which may become papular, or occasionally pustular; in the non-syphilitic, *no reaction occurs* and the procedure in such has no more effect than the injection of distilled water would have.

It has been pointed out repeatedly by Dr. Flexner and others that "the application of this test could by no possibility give syphilis to the patient, and, on the other hand, the test has now been used in hundreds of cases all over the world and has proved itself to be of the greatest value in diagnosing, and consequently in treating cases of a dangerous and obscure type." Despite such explanations the misrepresentation of

20. Noguchi, H.: A Cutaneous Reaction in Syphilis. Jour. Exper. Med., 1911, xiv, 557: Experimental Research in Syphilis, Tissue JOURNAL A. M. A., April 20, 1912, p. 1164.

every-day procedures in medicine is continued²¹ by these societies in the effort to support a propaganda of cruelty and ignorance.

Of new societies there is no end, but the presence in the community of individuals who will publish statements such as I have quoted suggests the need of a "Society for the Abatement of Preventable Ignorance."

OBSERVATIONS IN CEREBRAL LOCALIZATION

Another pamphlet entitled "Human Vivisection" put out by the American Antivivisection Society quotes several Americans concerning experimentation on animals in its relation to man, but gives no American observations except the Boston cases of lumbar puncture, which I have already discussed, and the study made in Cincinnati, in 1874, on cerebral localization. The latter is described as "one of the most horrible cases of human vivisection in this country, and one, too, which was terminated by the death of the victim." These observations were published under the title "Experimental Investigations into the Functions of the Human Brain."²² A patient with a loss of a portion of the bony skull was the subject of a study of the reactions following the insertion into the brain of insulated needle electrodes. The Antivivisection Society's report states that "an eroding ulcer had appeared which gradually laid bare the brain substance." It does not state, however, that this eroding ulcer was cancer (epithelioma) of thirteen months' duration, that from the excavation pus exuded, indicating a general suppurative inflammation of the dura, and possibly, also, of the finer meninges and the brain, and that at necropsy a thrombosis of the superior longitudinal sinus was found. It is distinctly stated in the original that "as portions of brain substance have been lost by injury or by the surgeon's knife, and the brain has been deeply penetrated by incisions made for the escape of pus, it was supposed that fine needles could be introduced without material injury to the cerebral matter." There is no statement concerning the consent of the patient, but on the other hand there is no evidence that

21. In connection with the luetin test, quotations are made also from articles by R. R. H. Gradwohl: Med. Rec., New York, 1912, lxxxi, 973; J. M. Wolfsohn: Bull. Johns Hopkins Hosp., 1912, xxiii, 223, and M. Cohen, Arch. Ophth., 1912, xl, 8.

22. Am. Jour. Med. Sc., 1874, lxvii, 305.

she objected or was coerced or intimidated in any way. In this connection, it is of interest that in the account of Observation 3 (testing of the posterior lobes) occurs the comment, "Notwithstanding the very evident pain from which she suffered, she smiled as if much amused." As the brain is an insensitive organ, the pain mentioned could not have been felt in it as the result of introducing needle electrodes; whatever pain was experienced must have been due to the peripheral effect of the stimulation. That "she smiled as if amused" shows that she did not object, that the pain was not severe and that no harm was done to her.

It is difficult, in view of the incomplete account, to pass judgment on this experience. The case was hopeless from the point of view of treatment—an extensive growth of cancer, a left-sided meningitis, with suppurating sinuses of the brain substance, indicated an early fatal termination.

If the patient under these circumstances consented to the observations described, it would appear to be a matter between herself and the physician making the observations. The symptoms which were present during the three days following the last (fourth) observation would appear to be due to the spontaneous lesions in the brain and not to the experimental procedure. This opinion is confirmed by the necropsy findings.

It is not an uncommon procedure in neurologic surgery to stimulate after operation, in conscious patients, certain areas of the brain. This procedure is a familiar one to all neurologists and it is therefore difficult to understand why so much has been made of these early observations in Cincinnati.

VAGARIES TAKEN SERIOUSLY

Another leaflet of the American Antivivisection Society contains the following:

I made the experiments on seventeen people between the ages of 15 and 30 years, but in no instance could a case of consumption, scarlet fever or small-pox be produced. These experiments were made in the following manner: I sprayed the poisons of diphtheria, small-pox, scarlet fever or consumption into the throat or nose or had them breathe them into the lungs, repeating the experiment in most cases every one or two weeks for months, with the result that no disease could be developed. Of course, I could not let the patients know what I was doing. I was supposed to be treating them for catarrh of the nose or throat.

'This statement is credited to *Life*, the New York *Herald* and the *Medical Brief* (April, 1906).

I have examined the original article²³ in the *Medical Brief* and find that the quotation is correct; but the paper in question is obviously written by a crank and it is not one from which a wise man would quote, though *Life* might have quoted more freely to the great amusement of its readers. For example, in the fourth chapter of this little effusion of four and a half pages, the writer pays his respects to the Darwinian theory in the following words:

I will explain one of these wonders in natural phenomena that is a stunner:

Take the human seed germs (spermatozoa), put them upon a plate, first spreading some alkaline nourishing substance upon the plate; for instance, a little soap, place the plate in a room of proper temperature, and in sixteen to twenty-four hours, swarms of ants will be running about. In other words, these living human germs placed under this different condition other than the mother soil, developed into ants. These little fellows can be watched and be seen to gradually develop, and start off on the run.

In Chapter II, this pseudoscientist thus disposes of the physiology of the circulation:

These experiments positively refute the assumption made by physiologists that the heart and muscular contraction of the arteries cause the blood to circulate in the body. They also prove that the circulation of the blood is governed by this law of attraction affinity, electricity, or call it what you will.

It is from Chapter III, entitled "No Impurities, Poisons or Germs can be taken into the Blood or System from Our Surroundings," that *Life*, the *Herald* and others have quoted. Immediately following the paragraph they quote, is the following explanation:

I want here to call attention to the fact that I did not make cultures of these poisons and germs, which is now considered so scientific, but in reality is unscientific and misleading. I used the genuine stuff, directly from the patients, sometimes carrying quantities of small-pox and scarlet-fever scales in my pocket for months.

That this individual actually lived in this twentieth century and said he did many of the things he describes

23. Rodermund, M. J.: Medical Wonders and Medical Blunders --a Story of Facts. Med. Brief, 1906, xxxiv, 279.

is undoubtedly true, for it is known that he went to one of our larger mid-Western cities and asserted that he had smeared himself with small-pox pus. Although he might have been held, through a liberal interpretation of the law, on the charge of carrying concealed deadly weapons, he was instead sent to the isolation hospital, where he and his clothes were disinfected and where he was kept isolated for a period of two weeks.

His books ("As It Is" and "Fads in the Practice of Medicine") show this individual to be without medical training in the modern sense. One of his letters to the commissioner of health of Milwaukee, as quoted by Dr. Forbes,²⁴ is illuminating as to his standing with medical editors. He writes:

I will admit that the *Medical Journal* would be the proper place for the discussion of these subjects, but I wish to inform you that for nearly six years that privilege has been denied me by nearly forty publications in the United States.

Some idea of his success as a practitioner may be gained from the fact that in a period of eight or nine years he tried to earn a living in four or five different places.²⁵ It is said that it was on account of his lack of practice and therefore his inability to do harm that he was not prosecuted for malpractice.

I have gone into this account somewhat in detail in order to show the non-science and indeed the utter nonsense which the antivivisectionists utilize in their attempt to oppose the progress of modern medicine. The individual under consideration may have attempted to introduce the materials he mentions into the respiratory passages of his patients, but to quote the acts of such a person, of unscientific training and apparently of unsound mind, as representative of the general practitioner, is as outrageous as were the stated inoculations.

WORKS OF KNOWLES AND HALES

Another account in a pamphlet of the American Antivivisection Society is that which refers to Dr. Knowles' observation on molluscum contagiosum.²⁶ In the course of an epidemic of this disease at St. Vincent's Home (Philadelphia) during the year 1908,

24. See letter of Alexander Forbes, *Life*, May 26, 1910.

25. Personal letter from a Milwaukee physician.

26. Knowles, F. C.: *Molluscum Contagiosum, Report of an Institutional Epidemic of Fifty-Nine Cases*, *THE JOURNAL A. M. A.*, Aug. 28, 1909, p. 671.

fifty-nine children were affected. In the hope of obtaining some knowledge concerning the causation and development of the disease, facts essential to its radical control, attempts were made to reproduce the disease in two children by rubbing the contents of the local lesion on an abraded surface. *Molluscum contagiosum* is a simple local condition in no way serious in its manifestations or consequences. Several physicians, among others, Retzius and Haab, have reproduced the disease on their own bodies. That Dr. Knowles should desire to repeat these experiments is, under the circumstances, hardly a matter for severe criticism.

The pamphlet of the British Union ("Experiments on Human Beings," by R. E. Dudgeon, M.D.) contains no reference to American and indeed none to English hospitals or physicians. Lawson Tait is quoted, and reference is made to Rev. Stephen Hales as "the originator of the modern practice of vivisection"; and it is recalled that this clergyman published a work on "Hemostatics," based on his observations on blood-pressure in the horse and other large animals. The fact is ignored that to-day every physician who practices accuracy of observation uses instruments which in their development go back to Hales' observations. It is cited that on the basis of these observations Hales obtained the approbation of the Royal Society, and that the society published his observations and made him one of its fellows. The account concludes, "His experiments have been utterly valueless as far as the health or life of human beings is concerned." It is of course possible that apparatus for taking blood-pressure would have been developed in any case, but it cannot be denied that Hales' experiments initiated and hastened this development.

VAGARIES OF RODERMUND AGAIN

It is of interest that the "Society for the Prevention of Abuse in Animal Experimentation," although it states in its "platform" that it regards "the abolition of vivisection as disastrous to legitimate scientific research,"²⁷ makes use of the same unfair and misleading methods as do the antivivisectionists who demand total abolition. It repeats *Life's* quotation about the spraying of the poison of scarlet fever, diph-

27. Pamphlet of the society.

theria and small-pox into the throats of patients, as do the American, New York and other antivivisection societies, without regard to the other absurd statements elsewhere in Rodermund's paper, which, if mentioned, would nullify, as they must realize, the importance of the part actually quoted. Their plea,²⁸ "We, the friends of vivisection, who desire to see it placed in the keeping of the most competent men, who are determined to take it altogether out of the hands of charlatans and tyros, have a right to ask a reconsideration on the part of the medical profession," is hardly convincing in view of the fact that they quote in support of their position a man discredited by the medical profession itself. This society, like the frankly anti-vivisection societies, makes much of what it considers to be experimentation on patients in hospitals. In a circular letter, under date of Jan. 2, 1914, over the names of the president (J. B. Y. Warner) and treasurer (Frederick P. Bellamy), it is stated, in referring to a new method of diagnosis, that "this is the natural sequence of unlimited animal experimentation. *Every physician in large practice knows this to be the fact.*" [Italics in original.]

In this connection, we have the opinion of one of the most prominent of European physicians, Dr. Joseph Bastianelli of Rome. After a prolonged visit to this country, devoted to a study of the methods of teaching and investigation in our hospitals, Dr. Bastianelli gratuitously offers the following:

Concerning the American hospitals, I am bound to say that every phase of the process of receiving and treating of a patient is characterized by strong sentiment and human sympathy. Patients are held as sacred. Everything is done to help them, regardless of creed and nationality. The hospitals are the best in the world, for rich and poor alike are cordially welcomed.

II. COOPERATION OF THE ANTIVIVISECTIONISTS WITH THE ANTIMEDICAL MOVEMENT

This brings us to one very significant fact in connection with the recent exhibit in Philadelphia—evidence of the apparent cooperation of the antivivisectionist forces with an organization having for its object opposition to the federal control of matters of public

28. From a pamphlet over the signature, "James H. Ecob" put out by the society.

health. Among other literature on the tables at the exhibit (Nov. 29 and Dec. 13, 1913) of the American Antivivisection Society were the publications (*Medical Freedom*, i, No. 2, and ii, Nos. 8 and 10) of the National League for Medical Freedom. These state that the object of the league is to "protect the people in one of their most sacred rights, the right of every man to select the practitioner of his choice in the hour of sickness"; but its real object, as is evident elsewhere in its pages, is to oppose the control by the federal government of matters of public health.

This is particularly emphasized in a pamphlet bearing the card of the National League for Medical Freedom, entitled "Evils of a Health Bureau," which attacks the American Medical Association and Senator Owen's bill to establish a national health board.

That there may be no doubt concerning the policy of the National League for Medical Freedom, let me quote from a leading article²⁹ by a director (William A. Davis) of the league. He says:

The greatest menace to the freedom of the people of the United States to-day is the activity of that portion of the medical profession which is attempting to establish a national Department of Health, with its chief executive officer a member of the President's cabinet, under the specious plea of advancing the "public health." . . . Its members are asking to establish a medical monopoly whose bands of iron have not been equaled since the dark ages.

In another number³⁰ Dr. Samuel G. Dixon, the head of the health department of the State of Pennsylvania, because he stated in an address that "compulsion, not persuasion, is the key-note of state medicine," is described as "the head of the paternalistic medical activities of Pennsylvania and a master spirit among the political doctors of the American Medical Association. . . ."

In other words, the league is opposed to government bureaus which might have charge of quarantine, health legislation, the control of water-supplies, sewage-disposal, pure-food regulations, and other problems which would thus have federal regulation and uniform enforcement. No matter what views one may have about states' rights or schools of medical practice, no

29. Davis, W. A.: Med. Freedom, ii. No. 10.

30. Med. Freedom, ii. No. 8.

one, I believe, who has the welfare of his fellow men at heart, desires to oppose regulations which tend to decrease disease in his own community or in that of his neighbor. The opponents of animal experimentation by distributing the literature of the League for Medical Freedom indicate that they are opposed to such humane effort and thus offer added proof of their opposition to the principle that the community at large should benefit by the fruits of medical investigation.³¹

I have gone into these matters in details for two reasons: First, that the medical profession should understand the animus which actuates such attacks, and secondly, that the general public should have a clear statement concerning the misrepresentation on which these attacks are based. "The public should definitely understand that the medical profession wholly repudiates and regards with abhorrence the employment of any procedure whatever which is in any way likely to injure rather than to benefit a patient who has entrusted himself, or who has been entrusted, to a physician's care."³²

The antivivisectionists charge that in experimental work the final test must be made on man. Of course it must. The object of all medical investigation is the relief of mankind's suffering from disease. After a method has been satisfactorily tested on animals, the final test must be on man, otherwise the preliminary work would have been without purpose. But in these first crucial tests on man the greatest caution is observed and it is usually the investigator himself who submits to the test. This was the case with Noguchi, who has been maligned by the antivivisectionists in connection with his luetin test. Before this test was put into general use Noguchi and other physicians who volunteered were subjects of experimentation. So also when salvarsan was first suggested for the treatment of relapsing fever; after tests had been made on dogs the assistants of Alt volunteered to take the injec-

31. It is significant that the *Medical Brief*, from which all the Antivivisection societies and the "Society for the Prevention of Abuse in Animal Experimentation" quote concerning the experiments of Rodermund on the spraying of poisons of scarlet fever, diphtheria, small-pox, etc., is controlled by one Henry R. Strong, who also publishes the *National Druggist*. Both these publications have for years been regarded as mouthpieces of the nostrum interests. The *Medical Brief* does not in any sense represent the views of scientific medical men.

32. The Washington Antivivisection Congress, editorial, *The JOURNAL A. M. A.*, Dec. 20, 1913, p. 2244.

tions in order to test the toxicity for man. Not until after this was done was it used on patients with relapsing fever, and of course later in syphilis.

This is the universal rule. As long as the problem at hand offers hope of solution by the use of animals, this procedure is followed. But once it is evident that man himself must be the experimental animal, the scientist volunteer is always ready. When it was evident that the problem of yellow fever could be settled only by the demonstration of the direct transmission of the disease from infected man to healthy man by the bite of the mosquito, Carroll and Lazear and soldier volunteers gave themselves willingly to the test. Lazear succumbed, but to the world was given the means of preventing the scourge of yellow fever. "Died in the service of his country" is the simplest phrasing which any people may use to honor its heroes; but to Lazear, as also to Ricketts, whose fatal illness was due to Mexican typhus which he was investigating, were given the immortal honor of dying in the service of humanity.

So also when in the course of the study of the transmission of malaria by the mosquito, the crucial test became necessary, two members (the younger Manson and Warren) of the staff of the London School of Tropical Medicine were ready to submit to the bite of infected mosquitoes brought from the Roman Campagna for that purpose.

This voluntary service of man is not limited, however, to the acute infectious diseases. It must be remembered that Henry Head's important studies of sensory disturbances due to nerve injury were based in part at least on a purposeful division of a nerve in his own arm, and aside from these major problems there are many minor problems in connection with which the investigator is himself constantly the subject of experimentation. These are instances in which the physician tests on himself a new procedure before he applies it—contrary to the contention of the opponents of medical research—to patients. Within the last two months two different clinical applications of experimental work have been tested thus by physicians in my department, and one of them not without severe results. Moreover, a vast number of experiments in physiologic chemistry and immunology are made with the investigator himself as the experimental animal.

I can recall that when the tuberculin eye-test (ophthalmic reaction) for tuberculosis, for the use of which some Philadelphia physicians have been severely criticized, was first announced, I and the staff of my laboratory (Bender Hygienic Laboratory, Albany, N. Y.), submitted to the test before using it on patients. Of the fourteen men, all physicians, to whom the test was applied, four had a positive reaction, that is, a congested or inflamed eye. These men did not look on this as a hardship, but rather were thankful that this evidence of latent or obscure tuberculosis somewhere in their bodies warned them of the necessity of care and appropriate treatment in preventing its further development.

Three courses are open to the medical profession:

1. To refuse absolutely to try any new drug, new operation or new means of diagnosis, because it would be an "experiment" and an example of "human vivisection."
2. To test new ideas, suggestions and methods at once on man.
3. To make the first tests and experiments on animals and then if found useful and not dangerous to apply them, with every possible safeguard, to the relief of man.

If the first course were followed, all progress would cease and all medical and surgical treatment would become stereotyped. The second involves a moral responsibility which few conscientious physicians would care to assume. The third has a basis in a definite ethical principle. Which would any sensible man or woman choose as a guide to medical progress?

2114 De Lancey Place.



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Animal Experimentation in the Diagnosis, Treatment and Prevention of Diseases of Children

RICHARD M. PEARCE, M.D.
PHILADELPHIA

DEFENSE OF RESEARCH SERIES PAMPHLET XXVII

Issued by the Bureau on Protection of Medical Research of the Council on Health and Public Instruction of the American Medical Association

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ANIMAL EXPERIMENTATION IN THE DIAGNOSIS, TREATMENT AND PREVENTION OF DISEASES OF CHILDREN *

RICHARD M. PEARCE, M.D.

PHILADELPHIA

An amplification of a fifteen-minute address before the American Humane Association on the occasion of its annual meeting at Atlantic City, Oct. 8, 1914. In the address, as originally presented, only tuberculosis and cretinism were used to illustrate the benefits to children of animal experimentation. For the purpose of the present pamphlet these illustrations have been multiplied by incorporating material previously utilized in a popular presentation of the subject. (*Public Ledger*, Philadelphia, May 14, 1914, Lesson No. 6, of Philadelphia County Medical Society.) For many suggestions in connection with the general subject I desire to acknowledge my indebtedness to papers read recently by Dr. Alfred Hand of Philadelphia and Dr. Henry Dwight Chapin of New York City before the Philadelphia Pediatric Society, and especially to Dr. Chapin for the courtesy of allowing me to examine his manuscript, part of which I have utilized without change of text. See Chapin, H. D.: What Animal Experimentation Has Done for Children. *Popular Sscience Monthly*, January, 1915, Vol. lxxxvi, p. 55.

Those who oppose animal experimentation do so on three grounds: First, that it is morally and ethically indefensible; second, that it is of no value in that it has not added to our knowledge of the diseases of man, and third, that it involves unpardonable cruelty.

As to the first of these, the moral and ethical right, the medical investigator claims that "Scientific men are under definite obligation to experiment on animals so far as that is the alternative to random and possibly harmful experimentation on human beings, and so far as such experimentation is a means of saving human life and of increasing human vigor and efficiency."

Now, if it can be shown that animal experimentation is of value, even if it be only in a single disease, in relieving the suffering of mankind, the claim that

* This paper is one of the series prepared for and reprinted by the Bureau for the Protection of Medical Research of the American Medical Association for circulation among the public. Twenty-seven of these pamphlets are now ready, taking up the relations of animal experimentation to ethics, diagnosis, cancer, vaccination, the live stock industry, tuberculosis, typhoid, dysentery, plague, rabies, surgery, internal secretions, the circulation of the blood, protozoan tropical diseases, etc.

animal experimentation is futile is rendered worthless, and at the same time the moral and ethical basis of the practice is established.

As your society is one which avows an interest in children as well as animals, and as a large share of its efforts is directed toward shielding children from the ill effects of their environment, I will, in support of the argument that animal experimentation is not futile, present examples of how animal experimentation contributes to the health and happiness of the child ; and I may add that the examples I offer are, for the most part, every-day procedures in the diagnosis and treatment of diseases of children — procedures of definitely known value.

In no field of medicine are the results of animal experimentation so easily demonstrable as in that of diseases of children. Children are especially liable to preventable diseases due to bacteria, and on such diseases bacteriology has in the past thirty years thrown a great flood of light, and the knowledge thus gained has not only greatly decreased the mortality of infancy and childhood, but also, as a result, has increased the expectancy of life.

That this general result has been obtained is a matter of popular knowledge, but the details of how it has been obtained and the share animal experimentation has had and is still having, is not always clear to the public. That animals were used in the original studies of the cause as well as the cure of diphtheria is well known, but few persons outside the medical profession know that animals are still necessary in many instances for the exact diagnosis of the disease, often for the determination of the duration of quarantine, and for the production and testing of diphtheria antitoxin. Therefore, with diphtheria, as with other preventable diseases, animal experimentation still acts to protect the individual and the public.

DIAGNOSIS

Tuberculosis.—Take, for example, in the field of diagnosis the case of tuberculosis, to which children are especially liable. This justly dreaded disease may occur as the well known “consumption” of the lung, or more frequently as obscure affections of the bones,

the joints, the lymph-glands or the coverings of the brain. Many of these conditions are difficult of diagnosis in the early stages. A lesion of the spine or of a joint may escape diagnosis until a hump-back child or a chronic hip disease is the result. Many tuberculous lesions simulate so closely other diseases that diagnosis cannot be made by the ordinary methods of inspection and physical examination, and exact knowledge of the condition is therefore delayed until the disease has so far progressed that successful treatment is difficult. Moreover, the direct microscopic examination of fluids or tissue from such diseases is not always of help, because in tuberculosis of the bones and joints, the lymph-glands and the cavities of the body, the tubercle bacilli are present in such small numbers that usually the microscope fails to reveal their presence. If, however, such fluid or tissue is injected into a guinea-pig, the bacilli present, be they ever so few, will cause tuberculosis to develop in the guinea-pig and thus establish a diagnosis. The importance of this test cannot be overestimated; not only does it ensure an exact diagnosis and therefore rational treatment, but time — perhaps the most important element when surgical intervention is demanded — is saved. Every year the fate of thousands of children depends on the use of guinea-pigs for this test.

Hydrophobia.—This disease is more common among children than adults, partly because of their close association with domestic animals, and partly because of their lack of judgment in the recognition of abnormal conditions in an animal. When a child, or an adult for that matter, is bitten, the question arises: Is the dog rabid or is he merely vicious or ill-tempered? If the physician in charge of the case realizes his responsibilities, the animal is found and killed — for whether rabid or vicious he is a menace to the community — and thus the sacrifice of the animal is recognized as a justifiable procedure, tending to protect the welfare of the public. But the symptoms of hydrophobia do not develop at once and the physician wants to know whether the child is to be treated for hydrophobia or merely by the usual antiseptic measures applicable to a wound of the skin. A tentative opinion may be reached if on microscopic examination of the brain of the dog are found the peculiar little bodies usually

associated with rabies and known as "Negri bodies." Experience has shown, however, that the surest test is the inoculation of rabbits with some tissue from the dog's brain. The development in such animals of the symptoms of rabies settles the question conclusively and thus the nature and extent of treatment of the human case under observation.

Syphilis.—The common form of this disease in children, the inherited or congenital form, is not always readily recognized. The disease may take many obscure phases and exact diagnosis, and therefore specific treatment, is impossible unless a certain specific test is made. This test (the Wassermann test), too technical to present in detail, requires every time it is made some fresh blood of the sheep as well as some serum of the guinea-pig. In all laboratories, usually those of hospitals, in which this test is performed, animals are kept for this purpose. In the case of the guinea-pig the animal is usually killed at the time of bleeding, but as only a small amount of sheep's blood is needed, these latter animals are kept for some time and are the subjects from time to time of repeated bleedings. Although the procedure is quite different from the inoculation experiments previously described, it is nevertheless a form of animal experimentation, and one without which the diagnosis of syphilis frequently could not be made. But this test has another value. It is a guide to treatment. As long as the disease is not cured the positive test persists. It is possible by repeating this test to determine by its permanent disappearance, the time when the child (or adult) is cured. This information can be obtained in no other way. What is true of the congenital disease is true also of the acquired, which, however, is relatively rare in children. The Wassermann reaction is therefore not only a diagnostic measure, but of value in prophylaxis as well, for its disappearance points to cure and therefore the impossibility of spreading infection. To obtain this valuable information, the use of animals to the extent of bleeding sheep and guinea-pigs is essential.

Diphtheria.—When a child has diphtheria the diagnosis may frequently be made as a result of the inspection of the throat (or nose). If this is impossible in most doubtful cases a bacteriologic study of cultures

from the throat clears up the diagnosis. In a small number of cases, most frequently diphtheria of the nasal passages, both these methods of diagnosis fail, usually because the appearance of the disease is not characteristic and the bacteria found differ from the true form of diphtheria bacillus. Under such circumstances, it is most important, for two reasons, to establish a diagnosis: (1) in order that, if the condition is diphtheria, the child may have the specific treatment — diphtheria antitoxin — and (2) that other children may be protected against an unrecognized case of diphtheria. Under such circumstances animal experimentation is the only resource. A guinea-pig is inoculated with bacteria from the throat or nose of the sick child and the diagnosis depends on whether or not the guinea-pig develops the characteristic symptoms and lesions of experimental diphtheria. But for still another important purpose is this test used in diphtheria. A regulation of the department of health requires that a child with diphtheria shall not be released from quarantine until bacteriologic examination shows the throat, or other part affected, to be free of diphtheria bacilli. The object of this, naturally, is to prevent the spread of the disease. Usually the bacilli disappear from the throat within a reasonable length of time, corresponding practically to complete convalescence and restoration to a condition allowing the child to take up its usual activities. Sometimes, however, the bacilli persist for an unusual period. The child is perfectly well and eager to go to school; the parents find the restrictions of quarantine irksome and rebel at the health regulations. But the child is still a source of infection; the community must be protected. There comes a time, if the bacilli persist for weeks or months, when the situation resolves itself into the practical question: "Are the persisting bacilli virulent and capable of causing disease?" To settle this point, an inoculation of guinea-pigs, as described above, is made. If the bacilli have no effect on the animals, quarantine, with certain precautions, is raised; if, however, the bacilli cause diphtheria in the experimental animals, the quarantine is maintained. The latter use of this animal test is not strictly speaking a diagnostic test, but it is one of the most important procedures in lessening the spread of diphtheria among children.

These examples of the use of animals in the diagnosis of diseases of children have been presented in some detail in order to bring out clearly the fact that these and many similar tests are as much a part of the armamentarium of the physician and surgeon as are the stethoscope and the clinical thermometer, or the scalpel and the Roentgen ray. More than that, they belong to the group of so-called specific tests, that is, a positive result indicates the exact nature of the disease. A guinea-pig developing tuberculosis after the injection of fluid from a diseased joint, means that the joint is tuberculous; a guinea-pig developing experimental diphtheria after receiving cultures from the throat of a child means that virulent diphtheria bacilli exist in the child's throat, and so on through the list of these specific tests. There can be no doubt, no question of interpretation. And it may be added that all these procedures are common, every-day procedures in diagnosis.

This list might be lengthened to include less frequent animal tests, as that for anthrax (a disease contracted from infected hides of cattle), glanders (contracted by contact with infected horses) and other diseases to which children as well as adults are susceptible. Also might be added the frequent use of animals, especially the guinea-pig, in the study of infected wounds, especially those from rusty nails, in connection with which it is of great importance to know whether the bacillus of lockjaw is present; but the examples given are sufficient to indicate the constant use of these valuable methods, without which diagnosis would not be the exact procedure which is the basis of modern scientific medicine.

TREATMENT

The most overwhelming proof of the value of a specific treatment is seen in connection with antitoxin in diphtheria. Before the introduction and use of antitoxin in 1895, diphtheria could truthfully be called one of the greatest scourges of childhood. With the increasing employment of antitoxin, however, the death-rate began to fall all over the civilized world.

The accompanying table (Table 1), quoted from Keen, gives the official reports of the mortality from diphtheria for every 100,000 inhabitants in certain

American and European cities before the use of anti-toxin and after its employment had become general:

TABLE 1.—MORTALITY FROM DIPHTHERIA
PER 100,000 INHABITANTS

	1894	1905
New York (Manhattan)....	158	38
Philadelphia	128	32
Baltimore	50	20
Boston	180	22
Brooklyn	173	43
Pittsburgh	64	26
London	66	12.2
Paris	40	6
Vienna	114	19

Dr. W. H. Park, of the New York City Board of Health, in a study of the average death-rate from diphtheria in nineteen large cities of the world in 1893 shows it to have been slightly over 80 per 100,000; in 1895, when the antitoxin treatment was introduced, it began to fall, and by 1907, when antitoxin was generally employed, the rate had dropped to 17 per 100,000.

In the London hospitals the mortality was reduced from 29 per cent. to 10 per cent. The same is true of other large hospitals of the world.

Table 2 shows the value of early treatment, as observed in the Hospital for Contagious Diseases in New York City:

TABLE 2.—DEATH RATE ACCORDING TO DAY
OF INJECTION

	Death Rate
218 cases treated on first day.....
1,153 cases treated on second day.....	4.59
880 cases treated on third day.....	12.50
598 cases treated on fourth day.....	16.40
351 cases treated on fifth day.....	14.24
694 cases treated after fifth day.....	14.15
	—
Total, 3,894 cases.....	10.57

Not only has the death-rate been much lowered, but the severity of the disease and its complications have been marvelously changed for the better. Perhaps this is best seen in the great diminution of the fatal and agonizing croup cases, where the false membrane descends into the windpipe and causes death by slow suffocation. At the Willard Parker Hospital, even the

late and neglected cases of croup that have not had the remedy before admission, now after a large, though belated, dose of antitoxin very rarely die from strangulation. If they succumb to other complications, they are at least mercifully spared the torture of prolonged suffocation. In this hospital, before antitoxin days, two-thirds of the croup patients that required a tube in the windpipe so as to prevent death from suffocation, died; now three-quarters are saved. It is hard to realize what such figures actually mean. In the years preceding the discovery of the germ that causes diphtheria and the working out of its antidote, among the cases reported of patients dying from diphtheria, more than 75 per cent. were attributed to diphtheria of the windpipe. Now, the antitoxin, when early and properly given, will not only cure in the great majority of cases, but those closely exposed to infection, as nurses and relatives of the sick, may be rendered immune by a single small dose of antitoxin. Over 35,000 cases were thus treated by the New York Board of Health without any serious sequel.

Cerebro-Spinal Meningitis.—One of the most fatal and distressing diseases, confined largely to children, is epidemic cerebrospinal meningitis. Before the working out of the antimeningitis serum by careful, scientific experimentation on animals, there was no method of preventing the growth and appalling effects of the micro-organisms that caused the disease. Now we have a serum that not only directly destroys or inhibits the growth of these germs, but also indirectly acts by stimulating the white blood-cells to overcome them, and at the same time a neutralizing action is exerted on the soluble and diffusible poisons that are produced. As a result, not only has the mortality been greatly lowered, but the severe symptoms and crippling complications have been most favorably influenced. The lowest mortality before the serum treatment ran from about 50 per cent. in sporadic cases to 75 per cent. in the epidemic form in different parts of the world. When the serum is now given by spinal (lumbar) puncture, the mortality drops to about 25 per cent. or even lower. If the serum is given early in the disease, the altered mortality is still more remarkable. The accompanying table (Table 3), quoted by Dunn from the studies of Dopter, shows this feature:

TABLE 3.—MORTALITY IN EPIDEMIC MENINGITIS
UNDER SERUM TREATMENT

Period of Injection	Cases Analyzed According to Period of Injection		
	Flexner Per Cent.	Netter Per Cent.	Dopter Per Cent.
First to third day.....	14.9	7.14	8.2
Fourth to seventh day..	22.0	11.1	14.4
Later than seventh day..	36.4	23.5	24.1

In accord with these is the experience of one hospital, the Children's Hospital of Boston, in which for many years a special study of meningitis had been made. During eight years Dr. Thomas Morgan Rotch had treated meningitis in various ways with a mortality varying from 60 to 80 per cent.; but the first year (Nov. 1, 1907, to Nov. 1, 1908) after he began the use of the Flexner serum he treated seventy-four patients, with a mortality of only 19 per cent.

In patients who recover the serum treatment not only shortens the duration of the disease — sometimes by several weeks — but lessens the chances of the terribly destructive sequels, such as hydrocephalus, blindness and deafness. On this point Dr. Dunn of the Children's Hospital of Boston, says:

The contrast in the appearance of the wards at the Children's Hospital in Boston now, and as compared with the preserum period, is a subject of general remark. Formerly there were almost always to be seen wasted little patients lying with head drawn back, neck rigid, limbs twisted and paralyzed, head swollen by hydrocephalus and other painful conditions, and remaining thus for weeks or months until death resulted. Now the little meningitis patients are soon laughing, talking and playing with other children, and need not to be kept long in the hospital.

Now through what means have these two great life-saving methods been gained? Solely through animal experimentation; at first, in the investigative stage, through the use of rabbits, guinea-pigs, horses and other animals, and at present the horse is still in daily use for the manufacture of these antitoxins, and the guinea-pig, especially in the cases of diphtheria antitoxin, is used for testing its potency. Animal experimentation is therefore as important a part of modern medicine as is the making and testing of drugs of vegetable or mineral origin, and this fact should not be overlooked by those who oppose animal experimentation as a means of research or investigation. It is the everyday means of procuring specific remedies

for the cure of diphtheria and epidemic meningitis, formerly two of the great scourges of childhood.

PROPYLAXIS OR PREVENTION OF DISEASE

Under this head, three procedures of great value, involving animal experimentation, may be discussed. These are the preventive treatment of hydrophobia and lockjaw and vaccination against small-pox. The first two are preventive in the sense that after the person is bitten or wounded, treatment is begun to prevent the development of symptoms; in the last the procedure is for the purpose of preventing infection.

Hydrophobia.—The Pasteur treatment consists in inoculating a bitten person at regular intervals for about twenty days with the altered virus of rabies—at first a very weak virus is used and later stronger virus until the person is immunized. As the immunization takes place it counteracts the virus formed at the site of the bite and the development of the disease is prevented. As the virus of rabies is localized to a large extent in the central nervous system, the material used in this treatment is an emulsion of the spinal cord. To prepare this so that it may be safely used, rabbits are inoculated with what is known as the "fixed" virus of rabies, and from the cords of such animals the weakened virus for treatment is prepared. It is essential, therefore, that if hydrophobia is to be properly treated, rabbits must be used.

Before the Pasteur treatment was introduced, the mortality among persons bitten by animals varied from 6 to 14 per cent. Since then the figures of the Pasteur Institute (from 1886 to 1907) show an annual mortality for twenty-one years of less than 1 per cent. Professor Law of the Cornell Veterinary School presents the accompanying table (Table 4):

TABLE 4.—RESULTS OF TREATMENT IN PERSONS BITTEN BY ANIMALS SUSPECTED AND PROVED RABID, RESPECTIVELY

	Number	Died	Per Cent.
Bitten by animals proved rabid by inoculation.....	2,872	20	0.69
Bitten by animals pronounced rabid by veterinarian.....	12,547	61	0.48
Bitten by animals suspected of rabies	4,747	15	0.31
Average mortality			0.46

In this connection it should be remembered that there is no known cure for rabies when symptoms have once appeared and that death follows a period of suffering, agonizing to the patient and harrowing to the observers.

Lockjaw.—This disease, known also as tetanus, and due to the bacillus of that name, is a disease with a definite incubation period and may for that reason be cured if treatment is begun immediately after the person is wounded. The serum which is used for this purpose is therefore usually described as a preventive rather than a curative serum, but sometimes fully developed cases, if mild or chronic, may be cured. This preventive treatment is particularly of value in the so-called "Fourth of July" injuries and has been largely responsible for the reduction of the mortality from tetanus formerly following our great national celebration.

The tetanus antitoxin is prepared in the commercial laboratories of our great drug firms by injecting horses with tetanus toxins, in the same way as diphtheria antitoxin is made. Also guinea-pigs are used to test its potency and purity.

Small-Pox.—Small-pox is essentially a disease of childhood, indeed at one time it was known as "child-pox." That it is peculiarly fatal to children is shown by the fact that in the great Montreal epidemic, with 3,164 deaths, 85 per cent. of these occurred in children under 10 years of age. As to the protection exerted by vaccination, Rotch has shown as the result of a study of small-pox in children in the city of Boston during a period of fifteen years, that no death occurred among vaccinated children under 5 years of age, while at the same time the mortality in the unvaccinated was 75 per cent. From the point of view of animal experimentation it is only necessary to add that this protection of children is gained by using the calf for the production of the vaccine and the guinea-pig for testing its purity. This last, it may be added, is of the greatest importance, for it is through such testing that a pure product is obtained and accidental infection with lockjaw and other diseases prevented.

Thus far have been described only those diagnostic, therapeutic and prophylactic measures, in the every-

day execution of which animals are and must be used. Many other procedures based on animal experiment are in use, but in these, animals were necessary only in the investigative stage; in their practical application the animal is no longer necessary. These, however, could not have been elaborated without the use of animals, and they stand as well-tried procedures, among the most important procedures of modern medicine. Two of these, the tuberculin and luetin tests, must be mentioned.

The *tuberculin reaction* depends on the principle that if a fluid in which tubercle bacilli have grown, and which therefore contains the chemical products of their growth, is injected into an animal or person suffering from tuberculosis, a transient increase of temperature occurs and constitutes the chief sign of a positive reaction; if no tuberculosis exists, no reaction occurs. The method is therefore of great value as a diagnostic test in obscure or doubtful cases of tuberculosis, and also is the generally recognized procedure in determining the presence of tuberculosis in cattle.

The fluid injected is called tuberculin, and as it is sterilized it contains no living bacteria and cannot cause tuberculosis. When the test was first used the tuberculin was injected beneath the skin with the aid of a hypodermic syringe, and the chief reaction which this method gives, is, as I have stated, an increase in temperature. Later it was found that if the diluted tuberculin was placed on the surface of the eye, there followed in tuberculous persons a reddening or congestion of the eye, which might go on to the stage of mild conjunctivitis ("pink eye"). This is known as the Calmette reaction. Still later it was discovered that if the skin was scraped, as in vaccination against small-pox, and the tuberculin applied over such an area, a local reddening — the von Pirquet reaction — could be obtained. There has never been any doubt about the value of the tuberculin reaction. It is one of the most valuable adjuvants in the diagnosis of doubtful tuberculosis.

The test has been much misrepresented by antivivisectionists, but without it, in very many children, tuberculosis would escape detection and proper treatment therefore be impossible.

Luetin is prepared from the micro-organism — *Spirochaeta pallida* — which causes syphilis. A suspension of this organism is so treated as to cause disintegration of the parasite. The material is then heated so as to ensure the death of all living material in the fluid. Phenol (carbolic acid) is added to prevent contamination, and the fluid — a sterile mixture — is injected into the skin, much in the manner employed in the tuberculin test. It is entirely devoid of living micro-organisms, as was shown by Noguchi, first on rabbits and monkeys, and later by applying it to his own skin and the skin of several physicians who volunteered for that purpose. The reaction in the syphilitic is a slight erythema (or reddening) which may become papular, or occasionally pustular; in the non-syphilitic, *no reaction occurs* and the procedure in such patients has no more effect than the injection of distilled water would have. This test has added greatly to the ease of recognizing obscure cases of syphilis.

Other tests might be mentioned, but these two must suffice to illustrate the typical diagnostic tests gained through animal experimentation, though in their application animals are no longer necessary.

Surgery.—But it is not in medicine alone that animal experimentation has been of value to children. Aseptic and antiseptic surgery are based on the solid rock of animal experimentation, and children have had their full share in the inestimable benefits that have followed modern surgical methods. Septicemia and pyemia are prevented and frequently cured. Cavities of the body formerly out of reach of surgical aid, are now fearlessly explored and life thus saved. As an example, the various obstructions of the bowel peculiar to children are cured in a large proportion of cases. In former times death usually ensued in such conditions, as both physician and surgeon feared the large mortality that followed the opening of the abdomen. Even very young infants are now successfully operated on for this grave condition.

Recently, bone grafting that promises brilliant results in straightening crooked backs and other bony deformities in children has been successfully tried as a result of previous experiments on animals.

Profuse and uncontrollable hemorrhages in the newborn, formerly fatal, are now saved by transfusion, which was first studied and the technic perfected by vessel-suturing in the lower animals. Practically the whole realm of surgical accidents and diseases in children has been benefited and illuminated, directly or indirectly, as a result of animal experimentation.

There is no foretelling to what extent disease can be overcome by persisting in the present fruitful methods. Already infantile paralysis is being hopefully studied as to cause and consequent cure. The same can be said of other crippling and fatal diseases.

Cretinism. — Even certain forms of idiocy have yielded to animal experiment. The scant relief possible for most forms of idiocy is well known to both physicians and laymen. In recent years one kind of mental defect has been explained and largely cured by a knowledge of the internal secretion of the thyroid gland. Formerly these individuals were doomed to remain semi-imbeciles. They were repulsive in appearance, with stunted growth, facial blankness, tongue protruding from half-open mouth, trunk large, with pendulous abdomen and short, stumpy limbs. A dull, apathetic mentality was always in evidence. An implantation of the thyroid in the abdominal cavity of dogs by Schiff showed that this gland would functionate even after its removal from its normal location. From this it was but a step to demonstrate that by administering an extract of the thyroid gland by the mouth the symptoms due to its abnormal absence in the child would be removed. The arrested, perverted growth and mental dullness, due directly to the absence of this important internal secretion, can thus be easily corrected by giving the dry extract from the thyroid of an animal. A whole class of hopeless defectives has thus been rehabilitated.

ANIMAL EXPERIMENTATION ENTITLED TO APPROVAL

These examples are sufficient, I think, to demonstrate to you that animal experimentation in your own field, that of child welfare, is not useless, and that medical practitioners and medical scientists are morally bound to continue their work in the hope of adding to our knowledge of other diseases, now little understood.

In this connection it is interesting to note that the foremost medical and scientific bodies of the world have passed resolutions supporting the practice of animal experimentation as a humane effort.

These societies are:

1892: The British Medical Association, representing the medical profession of the British Empire;

1908: The American Medical Association, representing the organized medical profession of the United States;

1908: The American Association for the Advancement of Science, representing all fields of science in the United States;

1913: The Federation of American Societies for Experimental Biology, representing the teachers in the biologic sciences in this country;

1913: The International Medical Congress, representing the medical profession of all nations.

It is worthy of note that against this opinion of the scientists and the organized medical profession of the entire world there is not a single record of a scientific body expressing the opposite opinion.

CRUELTY

No charge of cruelty in medical laboratories or research institutions has ever been sustained in a court of law, and in every instance in which charges have resulted in a libel suit the suit has gone against the antivivisectionists.

In this connection, with this question of the investigation of charges of cruelty, it is well to remember that in the report of the British Royal Commission on Vivisection, issued in 1912, the following statement may be found:

We desire to state that the harrowing descriptions of operations inflicted on animals, which are freely circulated by post, advertisement or otherwise, are in many cases calculated to mislead the public, so far as they suggest that the animals in question were not under an anesthetic. To represent that animals subject to experiments in this country are wantonly tortured would, in our opinion, be absolutely false.

The claim that anesthetics are not used is indeed as false as it is absurd, for it would be impossible in

the physiologic experiments usually cited in this connection to use with a struggling animal the delicate apparatus which such studies demand—apparatus so responsive that it registers the slightest change in position or movement. The same misrepresentation exists in connection with the oft-quoted reference to the use of curare.

I have worked in laboratories in Massachusetts, New York and Pennsylvania, and have visited most of the important laboratories of this country. With the exception of injection experiments, as used in investigations in bacteriology and immunity, and in feeding experiments, as in the study of nutrition, I have never myself made, nor have I seen, an experiment in which anesthesia was not used, and by anesthesia I mean complete anesthesia with ether or chloroform. As to curare, I have never seen it used, except in a single type of experiment, and that on frogs. I have never seen it used on warm-blooded animals, and have only once heard of it being so used, and in that instance ether was previously administered. Whatever may have been the practice with curare in European laboratories in the early days of physiology, I can truthfully say that in this day and country its use is practically limited to an occasional experiment on the frog.

Likewise the stories of insufficient food, improper quarters and neglect after treatment in recovery experiments are without adequate basis. Direct light, fresh air and proper food every investigator considers essential to the success of his experiment. It is to his advantage to keep his animals in the best possible condition. I have myself discharged, on the instant I discovered his offense, a laboratory attendant who neglected to feed, on one day only, the animals under his care, and in my experience all laboratory heads are especially zealous in their watch over the animals for which they are responsible.

A very significant thing in connection with these charges of cruelty is the fact that it is almost impossible to persuade the persons who make the charges to come to our laboratories and see the actual conditions. Since I came to Philadelphia in 1910 I have been particularly impressed with the false impression given the public through the exhibit and literature of our local

an vivisection society, and, therefore, personally and through the dean of our school, I invited the officers and members of the society to visit our laboratories. I believed that they were honestly laboring under a misapprehension as to facts and would gladly avail themselves of the opportunity of viewing our methods of experimentation. No one, however, during a period of three years responded to the invitation. Finally, last spring, when I repeated my invitation in a public lecture, two members of the local society came to my laboratory, were immediately admitted, saw an operation in progress at the time, inspected all our apparatus and visited the kennels in which were many animals, representing a great variety of experiments.

This experience I present in order to demonstrate to you that the so-called "closed door" of our so-called "halls of torture" is a myth. As far as my laboratory is concerned, the "closed door" does not exist, and I would like to take this occasion to invite any member of this association who is interested to visit my laboratories, with or without previous appointment; as he or she prefers.

I am willing to let our case rest with this brief presentation, but in the few minutes which remain I want to make a plea for both animals and children. Your society, as I understand its purpose, has two objects: the prevention of cruelty to children and the prevention of cruelty to animals. From your program I judge that you divide your activities equally between these objects, and that you judge each of equal value. Your efforts are directed almost solely against the human agent; that is, you protect the child or the animal from man's indifference, thoughtlessness or carelessness and from improper exploitation in commerce and industry. With the sufferings of the child, due to disease, you do not especially concern yourself; this you doubtless regard as a matter for hospitals, dispensaries and other medical social service agencies. Those of you who have much to do with investigating the conditions of children cannot, however, have escaped being impressed with the influence of disease in causing poverty, and is it not poverty that your agents in the vast majority of cases find to be the factor responsible for child neglect? Have not, therefore, the humane societies and the medical profession a com-

mon interest in this matter? Should not both support those individuals who endeavor, even though sometimes it be at the price of the sacrifice of animal life, to diminish disease and the poverty due to disease, and thus create a more favorable and happier environment for children?

The same plea may be made for the smaller domestic animals, the cat and the dog. The suffering of animals due to man's indifference or neglect is infinitesimal compared with that caused by their natural diseases; but no humane society, as far as I am aware, has attempted the study of the diseases of these animals. Money in considerable amounts is furnished by the federal government and by a considerable number of our states for the study of the diseases of animals of commercial value, or of importance to the industries. Our veterinary schools likewise engage in this work, but all these agencies have in mind the economic side, not the humane. One would expect the veterinary schools to study, for example, the diseases of the dog and cat, but in this country, unlike Germany, they have not, and they hasten to inform the public that they do not study experimentally the diseases of these animals, because if they did they would lose—so antagonistic has been the attitude of the antivivisectionists—support for their animal clinics. I am fully aware of the fact that a few humane societies have hospitals and dispensaries for the treatment of diseased and injured animals, but, so far as I am familiar with the situation in Philadelphia and New York, only a small number of animals are treated, few are treated free, and in no instance is a scientific effort made to reach a better understanding of the cause, course and cure of their diseases. I have tried to interest three of the local societies of Philadelphia in this matter, but have received no encouragement. Societies whose funds are largely expended in the wholesale destruction of stray and diseased animals cannot or will not see the advantage to be gained by cooperating with expert medical scientists in the study and treatment of animal diseases. One would think that the discovery of a means of preventing, combating or curing an animal disease would be the greatest triumph for which a humane society could labor. The only reason this ideal is not held is, apparently, the attitude of a few

individuals who oppose all experiments on animals, even though the experiments may be for the benefit of the animals themselves. Such an attitude cannot consistently or conscientiously be adopted by a national body whose efforts are truly humane, and I sincerely hope that the time will come when humane societies will be as much interested in preventing the sufferings of animals caused by disease as they are in preventing those for which man is responsible.

Your common interest in the child and the animal demands that you should *support* and *be supported* by the medical profession, and to this end there should be the closest cooperation in behalf of both child and animal; but if you will not cooperate with us in behalf of the animal, do not, by all that the present-day spirit of social service holds as progressive, altruistic and humane, obstruct *our* work in behalf of the child.



Biological Research: Its Value and Dangers

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DEFENSE OF RESEARCH SERIES PAMPHLET XXVIII

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"In the health of the people lies the wealth of the nation."

—Gladstone.

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CHICAGO



BIOLOGICAL RESEARCH; THE VALUE AND THE DANGER *

SAMUEL S. MAXWELL, PH.D.

Associate Professor of Physiology in the University of California

I seize with avidity the opportunity furnished me as your retiring president to discuss a subject which I am anxious should have your earnest consideration. *Biological research* includes many things. I mean to limit myself to those phases of it which require the experimental use of living animals. And I grasp this opportunity because I feel that our colleagues in other fields of scientific effort do not always fully perceive the value of the knowledge attained by this means ; and that they do not at all appreciate the danger that freedom of research in these lines may be seriously hampered by hostile legislation or misdirected public opinion.

You who are engaged in various lines of research will appreciate the fact that the immediate application of a discovery is no fair measure of its value ; the ultimate results of the knowledge obtained may become extremely far-reaching. It is in the creation of a background of knowledge and experience that the greatest good is to be obtained. Often we point with enthusiasm to certain noteworthy scientific achievements, and yet fail to perceive that these have become possible only through the accumulation of a multitude of small details, the results attained by the humdrum plodding of patient mediocrity.

The creative imagination of genius is creative, after all, only in the ability to make novel combinations of known elements. The successive steps in the progress of knowledge are absolutely essential. The difference between the genius and the common man is not that

* President's address before the California Chapter of the Sigma Xi, April 28, 1915.

* Reprinted from Science, N. S. 42, No. 1090, Nov. 19, 1915.

the former proceeds by longer steps, but that he takes them more rapidly—often so rapidly that he is hardly himself aware of the intermediate positions.

As an example of the results of the experimental method I want to speak first of the progress of knowledge of the circulatory system—the heart and blood vessels and their mode of functioning.

The beginning of definite scientific knowledge on this subject may be said to date from the publication by William Harvey in 1628, of "*De Motu Cordis et Sanguinis*," "The Movement of the Heart and Blood."

There was not lacking before the time of Harvey quite complete and accurate knowledge of anatomy of the organs of the circulation; the structure of the heart, the arrangement and distribution of the blood vessels, and the valves of the veins were well known. Notwithstanding this there existed in the minds of anatomists and medical men the most bizarre and remarkable explanations of the uses of these structures. I can perhaps illustrate no better than by a few quotations from Harvey showing the kind of notions against which he had to contend in teaching the doctrine of the circulation of the blood. In the Introduction to "*De Motu Cordis et Sanguinis*":

Did the arteries in their diastole take air into their cavities as commonly stated and in their systole emit fuliginous vapors by the same pores of the flesh and skin; and further did they in the time intermediate between the diastole and the systole, contain air, and at all times either air, or spirits or fuliginous vapors, what should then be said to Galen, who wrote a book on purpose to show that the arteries contained blood only? . . .

And if the arteries in their systole expel *fuliginous vapors* from their cavities through the pores of the flesh and skin, why not the *spirits*, which are said to be contained in these vessels, at the same time, since spirits are much more subtle than fuliginous vapors, or smoke?

But Harvey, instead of merely *speculating* upon the functions as they might be inferred from appearances in the dead animal, put everything possible to the test of *observation and experiment in the living animal*, and as a result was able to state his reasons for the belief in the circulation of the blood in language which can hardly be improved upon today. The different attitude of mind resulting from his practice of observation and experiment is shown in his assertion

That the facts cognizable by the senses wait upon no opinions, and that the works of nature bow to no antiquity; for indeed there is nothing more ancient or of higher authority than nature.

Contrast with this the views against which he had to strive as shown by another quotation from the same book:

Medical schools admit three kinds of spirits; the natural spirits flowing through the veins, the vital spirits through the arteries, and the animal spirits through the nerves. . . .

Farther, besides the three orders of influxive spirits adverted to, a like number of implanted or stationary spirits seem to be acknowledged; but we have found none of these spirits by dissection neither in the veins, nerves, arteries, nor other parts of living animals.

It was never permitted Harvey to know the exact method by which the blood passed from the terminations of the arteries to the beginnings of the veins; for no microscope suitable for the observation of the capillaries had then been invented. This final step was reached by Malpighi in 1661 just four years after Harvey's death.

After the fact of the circulation had been established, it began to be possible to investigate the mode of working of the circulatory apparatus. The first important step in this direction was taken by the Reverend Stephen Hales, a Church of England clergyman, who tied into the femoral artery of the horse a glass tube nine feet high and noted the height to which the blood rose. He was able to report an average pressure of the blood in the artery sufficient to support a column of liquid eight feet three inches in height, while the blood rose at the same time to less than one foot in the corresponding vein. He observed also fluctuations in pressure due to the individual heart beats, to the movements of respiration and to other causes. The details of his experiments were communicated to the Royal Society of which he was a fellow and were published in 1733 in a work entitled "Statistical Essays, Containing Haemostatics."

The method employed by Hales was extremely inconvenient on account of height of the tube. Moreover, it introduced a greatly disturbing factor, namely, the loss of blood from the vessels of the animal into the tube. These inconveniences were overcome by the use of the mercury manometer by Poiseuille (in 1828). But

the careful and detailed study of blood pressure dates from the invention by Ludwig (1847) of an exact method of recording blood pressures. From that time onward, not only in Ludwig's laboratory where many of the generation of physiologists just passing were trained in the methods of their science, but in all the physiological laboratories of the world has the study of blood pressure been continued.

It is impossible here to summarize all the facts of importance that have been the outgrowth of these investigations, and of others, connected with the functions of the circulatory system, and which could have been learned in no other way than by experiments on living animals.

The heart is a pump driving an incompressible liquid through a completely closed system of branching elastic tubes, the terminal connections of the outflow and inflow portions of the system being all of capillary size. The study of this system presents a series of difficult problems in hydrodynamics, in which all the relations of force, rate and output of the pump, the heart, and the pressure, and friction conditions in the arteries, veins and capillaries must be considered.

But this machinery is all composed of living tissues which are interacting and self regulatory to an extraordinary degree.

The discovery by Claude Bernard, and others, of the existence of vasomotor nerves through which the caliber of the arteries may be changed, regulated and controlled, thus adjusting the resistance to the ability of the heart, and also providing that the heavier flow of blood may be shunted from one set of organs to another according to the needs of the body, is of prime importance; so also was the discovery by Weber of the inhibitory action of the vagus nerve upon the heart, which, acting like a brake on that organ, keeps its action always under definite control; and the discovery by v. Cyon of the accelerator nerves whose function is in direct opposition to that of the vagus. Further, v. Cyon found that a special nerve, the depressor, carrying impulses from the heart and the great blood vessels to the brain, causes, when excited, a dilatation of the peripheral vessels and consequent reduction of the pressure against which the heart must work. None of these things could have been guessed from the study

of the anatomical structures, nor could they ever have been found out in any other way than by experiments on living animals.

But it may be asked, Has this knowledge any value? Has it any practical application? Is it useful only for the gratification of mere curiosity?

Putting aside for the present the implication in the expression "mere curiosity" which we hear so often in this connection I may answer that it is now possible to measure the blood pressure in man without resort to the method of Hales; no blood vessel has to be opened and no pain has to be inflicted. Blood pressure determination forms a part of every examination for life insurance, and of the routine of nearly every present-day medical examination. In certain conditions its measurement is of the most extreme importance. It gives exact, quantitative information on the state of the heart and blood vessels that could be obtained in no other way. And the usefulness of this information so far from being confined to diagnosis of disease of these organs themselves is quite as important in the light it throws on the functioning of other organs.

I have given this rather disproportionately long statement of the physiology of the circulation to make very specific what I mean in saying that the importance of most investigations is to be found not in the direct application of the specific discoveries but in the reflex effect of these on all related work. Anti-vivisectionists use the knowledge which has been obtained by experiments on living animals. No modern physician can for a single hour free himself from the deepest obligation to vivisection experiments, although he may never himself have made such experiments.

It is quite true that human blood pressure may now be determined without opening an artery and that the principles may now be explained without appeal to animal experiments; but I believe it to be equally true that this would not now be possible, and that neither the method of blood pressure determination nor its significance would now be known if the long series of vivisections had not first occurred.

In this connection it will be appropriate to say a word about surgical shock. Every one realizes that as surgery is practiced today the chance of coming out of

a major surgical operation is always good, yet it is no light matter; there is usually real danger; and the memory still remains with us of friends or acquaintances who in an otherwise not serious operation succumbed to shock. Shock is a peculiar complex not easy to define. There is not usually the suddenness which the word implies to the lay mind; but there is a great depression of the functional activities; and most marked of all its symptoms is an excessive fall of blood pressure. To discover the real nature of shock and thus to furnish the surgeon the means of its avoidance is no small boon to humanity. With this purpose in view many researches have been carried on. It has not been easy to find the true cause of the lowered blood pressure but much progress has been made. The investigators in this particular line have apparently been singled out as the objects of attacks of especial virulence, and are assailed with such terms as "brute," "savage," "arch fiend," "torturer," "devil in human form."

I have selected the history of the study of blood pressure on account of its comparative freedom from those details which appeal to the emotional and dramatic side of human nature. I have used it to illustrate the growth of knowledge sought for its own sake into knowledge which is applied to the good of man. But I have merely touched upon the latter. Let me emphasize again that the great importance is not in the value of this or that specific detail, but in the great background which has been built up, which enables us to gain and to interpret new knowledge, and to see things in a proper perspective.

The physiology of digestion might have served equally well to illustrate the same truths. We owe to Pawlow and other workers in this line a mass of knowledge of prime importance to man, and this could not have been obtained in any other way than by vivisection. It is true that a few unfortunate human beings have had gastric fistulas formed through accident, and they have been used to study processes going on in the living stomach. But these studies have had no such orderliness as those in which upon animals definitely planned and controllable operations have been made. Indeed, the human observations have been mainly useful to check up the observations on animals

and to see whether for some reason conclusions drawn from animals might not be wholly applicable to man.

To experiments on living animals we owe most of what is known of the functions of the various parts of the nervous system. The possibility of diagnosis of the seat of nerve tumors, of injuries, of pressure due to blood-clot and the like, in many instances depends upon knowledge of cerebral localization first discovered by experiment on the brain of the dog.

We are just now at the entrance into a new era in the history of physiological science. The study of the glands of internal secretion is widening and deepening our vision of the life processes, and I confidently believe that the next decade or two will be most fruitful in this comparatively new field of research. Already we have use of adrenalin, and various gland extracts. Nearly all our exact knowledge of this field is based on vivisection.

It is not the purpose of this paper to go into the enumeration of specific instances of the value of biological research; many of them are already familiar; some of them are, rightly considered, among the greatest achievements of the human race. You know that the event celebrated by the great Exposition whose lights are at this moment blazing across the Bay could not have been accomplished if malaria had not first been conquered through biological research; you know that Havana by the same means has been changed from a seed bed of yellow fever to a healthy port and has ceased to be a menace to our own southern coast. You know that while occasional deaths from diphtheria still occur, the intelligent use of antitoxin has dispelled the dread and the terror which its presence in any community formerly produced; that a knowledge of the Pasteur treatment for rabies has reduced the death rate from that horrible disease from 15 per cent. to about 0.3 of 1 per cent. These and the like achievements are what the Hon. Stephen Coleridge, honorary secretary of the English National Antivivisection Society, has eloquently denominated "*The desolating advance of science.*"

You know all these things and much more, of the *value* of the achievements of biological research. But you probably do not know or, knowing, do not realize the vigor of opposition to all this effort for the

advance of knowledge and the good of humanity. The *danger* of limiting, harmful restrictions is imminent and absolute prohibition is not improbable.

In England for years it has been necessary, if one wishes to perform a single vivisection experiment, to procure a license. It is much easier to get a license to run a low grogshop. Any man may without a license and with practically no regard for the sensations of the animals rip out the testes from a boar or dog, merely because it suits his convenience or his whim or his purse to have his animals gelded; but if a physiologist wishes to make the same operation for the purpose of scientific observation on the effects of castration he must secure a license stating with precision the building where this is to be done, and the purpose of the experiment, and he **MUST**, he has no option, perform the operation under complete anesthesia.

In this country at present the opponents of biological research point to England as the model country. But in England they continue the agitation for further regulation or complete prohibition, and they continue to persecute the licensees with persistent vilification and misrepresentation.

It would be out of place for me to take your time in a statement of the peculiarly extravagant and unscientific views of the opponents of biological and medical research if it were not that there is a real danger of the enactment of pernicious and obstructive legislation. A situation exists in which we who are doing what we believe to be an important work for humanity need your active cooperation, sympathy and support.

1. Practically all antivivisectionists agree in the charge that experiments on living animals are necessarily cruel.

Now cruelty implies the infliction of needless or avoidable pain. No one justifies or can justify cruelty in experimentation any more than he can justify cruelty in any other action. But in the question of pain the unbiased individual will see that no one is so well qualified to judge as the experienced physiologist or surgeon. It would require the whole evening to discuss this one subject. Allow me to point out in brief the following:

The experimenter, even if he were really cruel, would usually defeat his own ends by the infliction of

pain (*a*) because the pain impulses would cause disturbance of the normal functions which he seeks to discover and (*b*) because the struggles of a suffering animal would disturb the adjustment of apparatus and prevent the desired observation. It is the total ignorance of the real situation that causes so much emphasis to be laid upon this point by the opponents of research.

On the other hand, it is the fact that most vivisection experiments as actually performed, are done under deep anesthesia or narcosis—usually for obvious reasons much deeper than would dare be employed in human surgery. Now the opponents of research insist that anesthetics are not given, or that when given the attempt at anesthesia is a mere blind, and that the animals are allowed to undergo torture. Most of this discussion is by people who never gave an anesthetic, who would not know when an animal could be judged unconscious, and who would be unable to form an intelligent opinion as to whether movements of the animal were unconscious reflexes or purposeful struggles.

But why assume, as every one of the antivivisectionists does seem to assume, that all persons engaged in animal experimentation are necessarily cruel? As one reads their publications he finds that always the experimenter is supposed to delight in torture. In fact he is spoken of over and over again as "arch-fiend," "torturer," "devil in human form" and the like. Can they see no other purpose? No other motive? Has the eminent head of our department of pathology exposed himself week after week to the danger of infection with typhoid, tuberculosis and what not, merely because he has a fiendish delight in seeing the quivering of flesh and hearing the plaintive squeal of guinea-pigs when he thrusts the hypodermic into them? Why would not a plain needle serve equally? The point of view is so absurd that it should require no discussion among intelligent people.

It is charged, however, that the practice of vivisection tends to induce a disregard for the sufferings of animals and brutalizes the mind and conduct of the experimenter. Now it happens that I have a pretty wide acquaintance among physiologists, and I have known some of the most accused vivisectors rather intimately. Of course they are not all alike, they differ

as other men differ. But on the average in point of humane, kindly sympathy they stand above their colleagues. And the reason for this is clear to him who will listen to reason. They have gone into this work because the higher human sympathy has appealed to them; they have sought earnestly for those things which will relieve or prevent suffering; their lives are given to the solution of problems the ultimate end of which is found in the very things about which they are charged to be wholly indifferent.

Not only is it not true that vivisection experiments tend to make the experimenter callous; the reverse is actually the case. I can testify from my own experience that it is harder to make the fiftieth experiment than the first; that one's sympathies are more and more awakened rather than destroyed. Indeed, most of the stories told to illustrate the brutality of vivisectors in things aside from the experiments themselves are in the highest degree improbable. As, for example, the statement that Dr. Sweet, of the University of Pennsylvania, kicked across the basement floor a poor emaciated dog on which he had operated. An operated animal is too valuable to be used in this way.

Were I to descend to the methods of our detractors I might use the following from my own experience to prove that antivivisection doctrine induces brutality.

I was once teaching in a small college the president of which was an ardent antivivisectionist. One day I received by mail a large poisonous centipede, carelessly enclosed in an unlabeled box. I made haste to get it into a wide-mouthed bottle. I had just succeeded when the president came into the room followed by a stray dog. There was a rule that dogs were not to be allowed in these rooms. The president took me roughly to task for allowing the poor centipede to suffer for lack of air in the bottle. Then, seeing the dog, he asked if it was mine? When I told him it was not he ordered it out of the room. The poor animal instead of obeying crouched on the floor and the president kicked it brutally and cruelly across the room and through the entrance. Yet he could declaim with tearful voice upon Llewellyn's faithful hound Gelert!

It should be emphasized here that the lower animals themselves gain immensely from the results of vivisec-

tion and of experiments on living animals. The same advantages of protective serums and antitoxins are made available for them as for the human. The Agriculture Department of the University of California at the present time makes and distributes hog cholera serum. The Report of the College of Agriculture for the year 1913-14 states that when a herd of hogs becomes infected and is not treated with serum forty to eighty per cent. of the animals die. I am told by experienced and unprejudiced stock raisers that this estimate errs on the side of conservatism. The report shows further the following figures for a diseased herd treated with the serum:

Died before vaccination.....	92
Sick when vaccinated.....	123
Number vaccinated	1,656
Died after vaccination.....	233
Per cent. of loss.....	19

That is the conservative statement of the report. There should actually be deducted the 123 sick when vaccinated, for vaccination does not help those already sick with the disease. That reduces the percentage to 15 as compared with 40 to 80 per cent. when unvaccinated.

Now the vaccine can not be prepared without operation on living animals; and the method and the underlying idea could never have been reached except through animal experimentation.

This may serve as a near-by example of what is done and as a forecast of what will be done for the animals themselves. The very beginning of Pasteur's famous work was for the conservation of animal health. *To this really great end none of the opponents of vivisection has contributed an iota.*

2. It is affirmed by most antivivisectionists that experiments on animals are useless in that no knowledge of any real value has ever been attained in that way. This attitude is well illustrated in a recent circular entitled "Claim Everything," issued by the American Antivivisection Society. This circular is intended to be a rebuttal to an article by Dr. W. W. Keen in the *Scientific American* of June 20, 1914. The statements in the circular are on the authority of the

president of the British Union for the Abolition of Vivisection. The circular says,

Brain surgery owes nothing to animal experimentation. In brain, above all, the animal differs from man.

This appeals to a multitude of voters who do not know that motor localization was discovered by Fritsch and Hitzig on the brain of a dog. Dr. Keen had referred to the new and highly successful methods of direct transfusion of blood. The circular states,

The direct transfusion of blood needs no experiments with animals, nor is the operation itself necessary.

The curious psychological twist in the reasoning of the opponents of progress in scientific medicine is shown in the following quotations from the same circular, copied verbatim, except that to save the space of comment I have inserted the italics:

Operations for goiter, again, depend upon the *aseptic treatment*.

Diphtheria has been reduced solely by *sanitary measures*.

Malaria has been abolished by *sanitation*.

Yellow fever can not have been abolished by any means based on experiments on animals, *because the germ has never been found* to experiment with.

Discovery of salvarsan. This had better never have been made.

Every one familiar with the history of hygiene and sanitation knows how much of our knowledge and our point of view has been obtained through experiments on animals. Prohibit animal experimentation and progress in hygiene and sanitation would be practically brought to a standstill. Yet the opponents of research reiterate the statement that hygiene and not experimentation has enabled us to advance, and hence that experimentation is useless. Where a forward step has been made which is not attributable to "hygiene," as in the case of direct blood transfusion, its usefulness is flatly denied.

In most literature of this kind you will find expressed or implied a denial of the whole range of scientific knowledge as to the relation of microbes to disease. They refer to serums, vaccines and antitoxins in terms of profound contempt such as "rotten animal pus."

3. Another argument is based on the so-called "rights of animals." As a question of theoretical ethics I am willing to leave that for the present to the philosophers. I can not argue with the man who insists that his dog and his hog are as good as he is; that he has no right to restrain the one or to eat the other. If he refuse to eat meat, or eggs, drink milk, use leather, wool or other animal products for clothing or shelter; if he refuse to make counter attacks against the lions or serpents which attack him, he is consistent; I cannot argue with him; I can merely watch him go his way in the procession with the trilobite, the ichthyosaurus and the dodo. But intensely practical questions arise and must be met. And the life of a relatively few animals is placed against the life and health and comfort of the human race. The antivivisectionist insists that even if you grant that the injury to the guinea-pig or the rabbit or the horse will save the life of a child you have no right to save it in that way. If there is no room in the life-boat for the woman and the dog you have no right to push out the dog to make room for the woman.

But here I want to take issue squarely with the claim that we have no right to make experiments which cause pain — that is a fatal admission which some of the English physiologists have made. We have a right to perform painful experiments if the knowledge that we seek can be obtained in no other way. Ordinarily it can be obtained better without pain, or can only be obtained in the absence of pain, but the principle remains. So long as man lives in the same world with other animals, eating to some extent the same food, subject to a large extent to the same diseases, it will be necessary for man either to maintain the mastery or to become one of the beasts of the field himself.

But especially I can not see why experiments for the good of humanity and for the benefit of the animals themselves should be prohibited on the ground of cruelty and the absence of right, in the light of the permission of many other things. The castration of an animal as performed on the farm by far exceeds in pain and callousness of performance anything which I have ever witnessed in a laboratory. A few hundred animals are used in all our laboratories for all purposes. The census report shows that in California in

1909, there were born 163,728 bull calves. It is fair to assume that 150,000 were castrated. There were born 41,927 colts. Of these approximately one half were probably males, and making deductions for those kept as stallions, there were here at the lowest estimate 19,000 geldings. There were 283,741 pigs born, which means probably 135,000 males to have their testes ripped out. A total each year in California of 304,000 operations. Comparing these in number and violence with the work in biological laboratories and medical schools, the latter becomes wholly insignificant. But the gelding of the boar does not have the emotional appeal in it and we hear little about it. Dehorning of cattle is a painful operation, but it saves vastly more pain which would result from the injury which, without it, they would inflict upon one another.

4. It is urged that certain results of undoubted value (or from the standpoint of the opponents of research, of possible value) could have been reached by some other way. This is a line of reasoning which has been used with a great flourish of apparent candor and show of plausibility. A biologist having by a long and painstaking series of experiments found the solution of a problem, a pettifogger takes that solution and shows by a play on words, how he could, without experiment, have derived the same conclusion from certain given data. This is the basis of the constant appeal to hygiene, as the means of prevention of disease; while the very principles of hygiene are based throughout on animal experimentation.

I have read recently with great interest two books, accounts of journeys over practically the same ground, the journey from Mombasa on the East African coast to the great lakes at the source of the Nile. The one is by Lieutenant Speke, the other by Colonel Roosevelt. Speke traveled in constant danger and discomfort, beset with discouragements and the opposition of treacherous natives, in an unexplored, unknown land. Roosevelt made the trip by railroad. Our antivivisection opponents continually upbraid us for traveling like Speke in the difficult, uncharted territory, when we might wait and go *de luxe* in a Pullman: Will they build the road while we wait?

5. A further charge is urged against vivisection, that it leads to a state of mind which will not hesitate to

make similar experiments on man. Human vivisection is held up as the acme of fiendish impulses of the biologist, physiologist or surgeon. A hospital is a place of unspeakable horrors.

Now on this I must make two remarks: (1) That any thinking man will see that certain observations may be made on a patient without injury or pain to the patient, and that if these observations or experiments furnish useful knowledge, there can be no possible objection to them, and (2) every surgical operation is a vivisection experiment in one sense. A surgical friend has vivisected me, and yet I do not call him a fiend and an arch torturer.

Of course there are all sorts of men among physicians and surgeons as in all other professions. Abuses and outrages do occur, no doubt. There have been wicked doctors who have abused their trust; and there have been clergymen with whom the virtue of a young lady boarder was not safe; but we need not say for this reason that all surgeons are arch torturers and that all preachers are arch lechers.

And this brings me to a point I wish to insist upon, that just as you do not need to pass a special law against adultery by ministers of the gospel, but that if you did so you would put an imputation on the character of a large body of earnest, sincere and unselfish men, so you should not pass laws which would put on men in biological research the imputation of bad faith and cruelty. Make the general laws against cruelty to animals as strict and far-reaching as may seem necessary for the good of the human race; but do not single out the men who are devoting their lives to the search after that knowledge which is for the best good of the race, and make them the special objects of unnecessary, restrictive limitations. If experiments on animals must be prohibited let the same law prohibit castration of animals and the dehorning of cattle. If the English law requiring all operations by a scientific man to be done under anesthesia be adopted, then require that the operations on the farm be performed in the same way.

You will perhaps say that the arguments mentioned are unworthy of attention; that it is beneath our dignity to answer them. It will not do to take that attitude. The opponents of research are too strong and

too well organized to be neglected. They have enormous sums of money at their disposal. They have been able to subsidize newspapers and are prepared for a campaign of persecution and prosecution. The opponents of research are not easy to classify. They represent widely varied types of mind, but the following are usually recognizable:

1. The fanatics. This type is represented by the man who states over his signature that he would prefer to have his own child die of diphtheria rather than to have it saved by the torture (?) of a single guinea-pig. These are perhaps the only thoroughly consistent antivivisectionists. They are often so much in earnest that they do not hesitate to mislead the public through publication of untruths.

2. The cultured ignoramuses. A large class of people highly educated along certain lines of language and literature, but profoundly ignorant of the most simple and fundamental facts of natural law. They are the Clara Vere de Veres of both sexes and all ages.

3. The financially interested. Great fortunes are accumulated by the sale of patent nostrums. The business makes headway in proportion as medical knowledge and medical practice can be thrown into disrepute. Thus the *Journal of Zoophily*, January, 1915, quotes the following with no word of disapproval:

Medical Freedom says in its October number:

"Only recently Mrs. Catherine E. Mercer and her two children were vaccinated against typhoid in Brooklyn, N. Y. All were made ill. Mrs. Mercer died and the two children suffered for weeks. In Iowa a perfectly healthy guardsman was vaccinated against typhoid, became ill and died. In Camp Dodge, Des Moines, Iowa, Conrad Liljeberg died soon after vaccination. Also Clarence Pantzer, Thirteenth Coast Artillery, National Guard, New York."

4. Religious cults. It must be said to the credit of the majority of those who profess a religious philosophy which ignores disease that they are not inclined to put obstacles in the way of medical progress. Nevertheless, in a recent number of the *Journal of Zoophily*, a column headed Anti-Vivisection Notes is entirely occupied by a long tirade against the medical profession by a well known subscriber to a belief of that type.

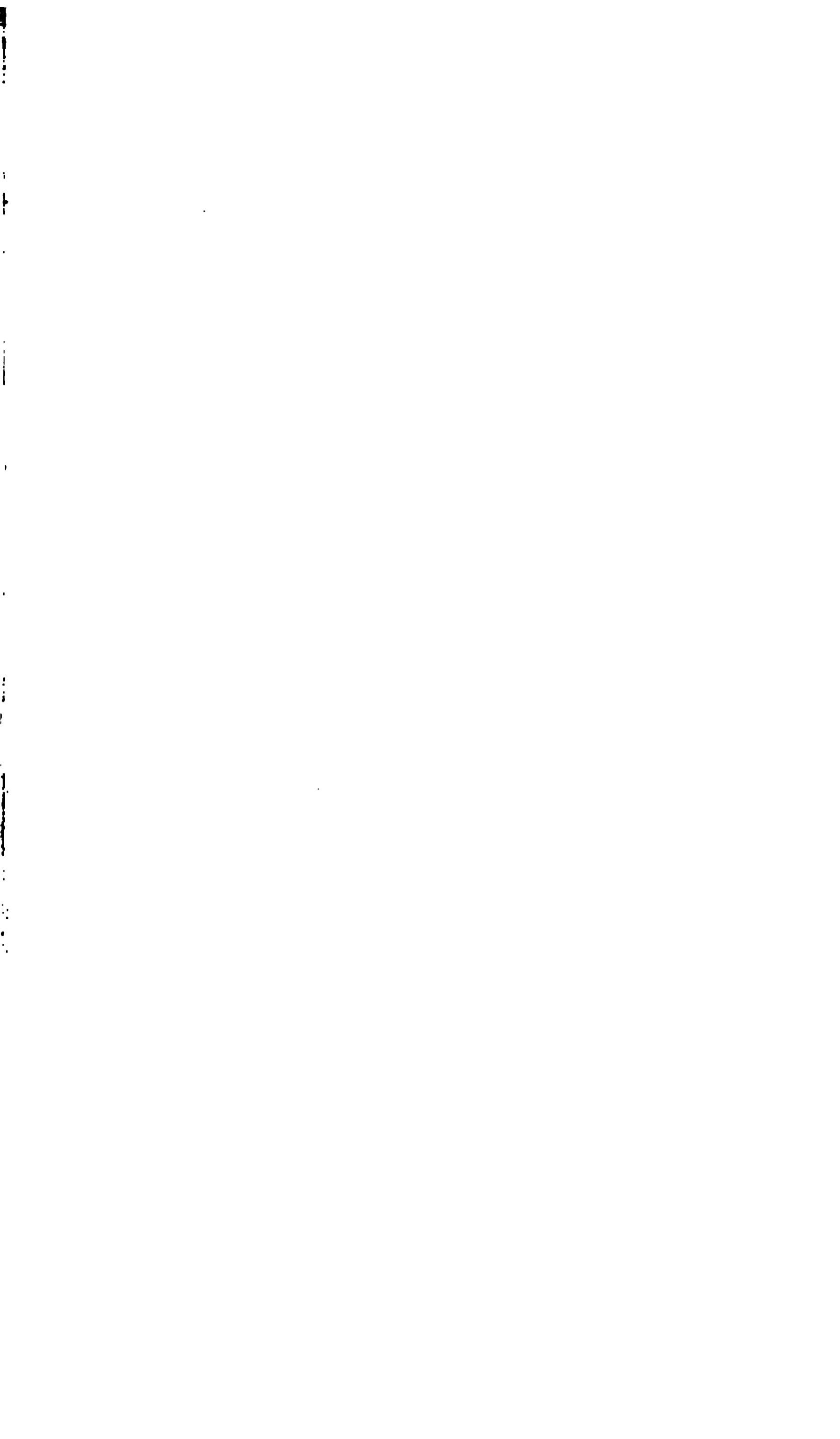
5. Demagogues. There has never been wanting a class of pretenders who masquerading as reformers and philanthropists succeed in getting themselves into legislative positions. Such imposters find an appeal to prejudice and emotion a powerful factor in securing the support and good will of the uninformed but well-meaning public.

The above are strange bedfellows, but they seem to agree well among themselves. They have this more or less in common that they desire to throw the efforts of the earnest, honest physician into disrepute; his loss is their gain. Anything does for a pretext. It can be vivisection or vaccination or quarantine or what not. Their method is always that of the pettifogger or the demagogue. They publish accounts of experiments done under anesthesia and of experiments done before the introduction of anesthetics as if they were all alike and now all in vogue. They describe vivisections done in the days when men were hanged and quartered as if they were the common practice of today. And in it all the appeal is to sentiment and prejudice, not to reason and common sense. By these methods they reach and may yet more effectively influence large numbers of honest and conscientious voters too busy to inform themselves as to the real issues, and unable to unravel the tangle of sophistry, sentiment and misrepresentation, with the result that there is great danger of hostile and harmful legislation.

In the face of all this opposition I feel justified in calling for support from you who are working in the various fields of science more or less remote from that of biology, not only because as co-workers in the effort to enlarge the sphere of human knowledge as men of open mind and enlightened sympathies your support may rightly be expected by those whose researches are primarily concerned in the discovery of those truths that are directly applicable to the diminution of pain and suffering and disease; but I would also place before you the importance to all of you in your various fields of that which I have called the larger background of knowledge. It is only by this that we can see things in their true perspective. Our respective sciences and our special fields of research become of value only when their wider relations are apprehended. And may I without unduly magnifying my office as a biologist

call your attention to the fact that biology has contributed no unworthy share to the means of progress in the sister sciences. The contributions of biologists, especially the workers in physiological chemistry, to the general advance of chemical science does not require to be mentioned; nor do I need to refer to the usefulness to physical chemistry of the fertile ideas of Pfeffer and De Vries in the explanation of osmotic pressure. The physicists do not need to be told that by far the most sensitive galvanometer for the measurement of minute currents of short duration is the device of the physiologist Einthoven, designed primarily for use in the study of living organs. The engineers will recall that the method of recording progressive changes on a revolving drum is the application of the kymographion invented by Ludwig for the recording of blood pressures but now employed in securing graphic records of a great variety of natural phenomena.

Or let me reverse the picture and remind you that the physiologist, the pathologist and the physician are laboring to apply the results of your researches in the explanation of the normal life processes, and to use them in the discovery of the causes of pain and suffering and disease, to the end that these causes may be overcome. Toward this result all lines of scientific effort are contributory.



DRUGS AND ANIMAL EXPERIMENTATION

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DEFENSE OF RESEARCH SERIES PAMPHLET XXIX

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DRUGS AND ANIMAL EXPERIMENTATION

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The origin of the belief of mankind in the efficacy of drugs in the treatment of disease is a most interesting subject for speculation. The use of drugs antedates written accounts. Certainly the most primitive people on the earth today employ drugs as curative agents, and the earliest written records tell of the uses of drugs and poisons. We know that at certain periods disease was looked on as evidence of displeasure of the supreme being or beings, and that it was in the nature of a punishment visited upon man.

The view has been expressed that, since many of the materials used as remedies are disagreeable, either in odor, taste, texture or their origin, the taking of the medicine was of the nature of a sacrifice to appease the gods. The fact that not all of the materials used by primitive people are abhorrent is opposed to this view. Again, the belief in the efficacy of drugs may be attributed to the view which seems to have been held that since the supreme being created all things, including man, and sent the diseases to plague him, he must have created a remedy for every disease and left it to the ingenuity of man to discover the remedy. In the writings of the renowned Paracelsus¹ (1493-1541) occurs the statement: "Every disease has its medicine. For it is God's will that He be manifested in marvelous ways to the sick."

1. Paracelsus: Die erste Defension, 1:253, quoted from Stillmann: Paracelsus, Chicago, The Open Court Publishing Company, 1920, p. 123.

On the other hand, the belief in the efficacy of drugs, even in very early times, may have been based on observation and experience. Primitive man must have come in contact very early with strong pharmacologic agents, such as fruit juices, which, on being left exposed to the air, had fermented and yielded alcohol. He must have observed the effects of such materials. Similarly, among the plants, he must have found drugs which produced such remarkable effects that they would not escape the crudest observer. When he found substances which taken internally or placed on the skin produced decided effects on his body, nothing could have been more natural than for him to use such materials in treating injuries and illness in order to effect desirable changes within him. When illness plagued a man, he and his friends searched for a remedy as long as life lasted, and in the course of human history it is probable that almost every accessible material has been used in the treatment of disease.

The observations made on the action of the drugs in disease were crude and faulty, and no one knew what the course of the untreated disease would be, because all patients were given remedies. Yet, by this method, most valuable advances were made in the course of the ages. Thus, opium was in use before the Christian era, mercury was used in the treatment of syphilis in the sixteenth century, and cinchona bark, from which quinin is derived, was employed in the treatment of malaria in the seventeenth century. At the time of the Spanish conquest, the Indians of Peru were using coca leaves to assuage the pangs of thirst and hunger in their long journeys over the Andes. The action of the coca leaves, we now know, is due to the cocaine which they contain, which acted partly as a local anesthetic and partly as a stimulant of the central nervous system.

The difficulty with this method was that it took many hundreds of years to advance the healing art with a definite contribution, and even then the value of the remedy in most cases was not actually proved, but was still a

matter of opinion. Innumerable examples could be given to illustrate the increased value a drug possesses when its use passes from a haphazard to a scientific basis. We shall return to this subject later in this discussion.

Therapeutic investigation differs from most other types of work in that one cannot both treat an individual and leave him untreated excepting in certain diseases confined to the surface of the body. In other words we cannot divide an individual and treat half of him, and leave the other half untreated in order to determine definitely the effects of a drug under identical conditions. When we use different individuals, it is impossible to have conditions identical because two individuals may not respond in exactly the same way to a given disease or a given remedy, so that in all cases a therapeutic agent must be subjected to examination in a very large number of individuals under the best controlled conditions possible in order to get a final estimate of its therapeutic efficiency. Just as certain individuals may show an idiosyncrasy toward a drug and respond differently from the average of the same species, so there are certain differences in the response of different species to substances. The idiosyncrasy of certain species toward certain substances is well known and recognized. Apart from the remarkable variation in the response to drugs, noted in the case of certain species, there is a remarkable similarity in the response of the whole animal series toward drugs in general.

THE EFFECTS OF VARIOUS DRUGS ON MAN AND ANIMALS IS SIMILAR

The statement is frequently made in anti-vivisection publications than man and animals are so dissimilar in their reaction to drugs that no information of service in human medicine is derivable from studies of the action of drugs on animals. Such a statement has never been made or implied by any one having first hand knowledge of the subject. Let us examine the facts for a few of the most important drugs.

General and Local Anesthetics.—The most useful and safest general anesthetics for man are also the best and safest for the animals, and are in daily use whenever operations are performed on man or any of the higher animals. Can it be denied that the action of this group of substances on man and dog, for instance, is essentially identical? In the anesthetizing of the two, we employ the same agents and apparatus. Both pass through the same four stages under chloroform or ether, namely: (1) slightly impaired consciousness; (2) stage of excitement; (3) surgical anesthesia, and (4) toxic stage approaching death. The changes occurring in the circulation and respiration in chloroform and ether anesthesia are essentially the same in man and in dog. Similarly, the local anesthetics have the same effects in animals and in man. Thus, cocaine placed in the eye of the dog or rabbit takes away the sensibility, and touching the eyeball no longer causes the animal to wink. All of the local anesthetics have been introduced through animal experimentation. For many types of operation in human surgery, they possess a great advantage over the general anesthetics.

Soporifics (sleep-producing drugs).—The sleep-producing drugs for man act entirely similar in the case of the higher animals. They produce sleep of a depth and duration depending on the dosage. As in man, an excessive dosage of these drugs will produce anesthesia. The soporific action of every member of this group of drugs was discovered by animal experimentation, and then used therapeutically.

Strychnin.—This substance acts essentially the same in the animal series from the frog to man. The drug in every case causes increased excitability of the spinal cord, so that ordinary sensory stimuli reaching the cord through the nerves carrying sensation cause convulsions which follow one another at intervals depending on the dose received and the rate of absorption. These convulsions in the frog, rabbit, dog or man can be produced by stimulating sensory nerves, and in the frog they can be largely

prevented by cocaineizing the skin. Cocain is absorbed through the intact skin of the frog. In treating strychnin poisoning in man, we apply the information gained through animal experimentation, largely with the frog; and although it is not practical to cocaineize the entire surface of the body of a man, we keep the patient in a dark room free of all noise and vibrations, and protect him as far as possible from sensory stimulation.

The dose of strychnin for each kilogram of body weight necessary to kill many animals, including man, is known. The minimal fatal dose for the commoner forms is given in Table 1.

TABLE 1.—MINIMAL FATAL DOSE OF STRYCHNIN

Animal	Mode of Administration	Minimal Fatal Dose per Kilogram Mg.
Rat.....	Subcutaneously.....	3.0
Frog.....	Subcutaneously.....	2.1
Mouse.....	Subcutaneously.....	1.3
Man.....	By mouth*.....	1.1
Ground squirrel.....	Subcutaneously.....	0.8
Rabbit.....	Subcutaneously.....	0.6
Cat.....	Subcutaneously.....	0.4
Dog.....	Subcutaneously.....	0.4

* It is probable that the fatal dose of strychnin for man by mouth is very nearly the same as it would be if given subcutaneously.

The minimal fatal dose of strychnin for man is arrived at through the many cases of murder, attempted murder, suicide and accident. Thus, not only the symptoms of strychnin poisoning, but also the fatal dose per unit of body weight is similar for man and the animals mentioned. So true is that that, in cases of poisoning, the toxicologist ordinarily tries the effect of the material isolated from the dead body on the frog—an important test in the identification of strychnin. The test is always recognized by the court. It is true that there are other species that are very much more resistant to strychnin than are man and the common test animals. Thus, the dose necessary to kill a snake is 23 mg. per kilogram, and for the bat, 40 mg. per kilogram. The amount of a substance that is required to kill an individual of one species

may be much greater than for an individual of another species, and yet the type of action may be the same in the two cases. The fatal dose is only one of a number of important facts to be ascertained.

Atropin.—There are several instances in which the susceptibility of a particular species to a drug departs very far from that of the remainder of the animal series, and a case that is frequently referred to is the high degree of tolerance of the rabbit to *atropa belladonna* and the constituent atropin.

The action of atropin has been studied on certain beetles, amphibia (salamander, triton and others), the frog, guinea-pig, hedgehog, rat, rabbit, chicken, pigeon, dog and cat. Among the mammals, there is little difference in the symptoms produced, but marked differences in the dose required to produce similar effects. Man is the most sensitive creature to this drug; then in order come the carnivora and finally the herbivora. The rodents are particularly resistant to atropin.

Atropin and belladonna are very valuable drugs in human medicine. They are used:

1. To dilate the pupils for ophthalmoscopic examination and to prevent permanent damage in iritis.
2. To lessen vagal inhibition of the heart in certain cases of arrhythmia and to prevent reflex stoppage of the heart and death in certain conditions, such as in early chloroform anesthesia.
3. To reduce the secretory and motor activity of the stomach in gastric and duodenal ulcer, and to distinguish between pyloric occlusion of the stomach by spasm of the pylorus, which does not require operative procedure, and organic obstruction, which requires immediate surgical intervention.
4. To dilate the bronchoconstrictor muscles in asthma and in anaphylaxis and allied conditions, in which it may be life saving.

The first use mentioned did not require animal experimentation. The second use could never have been discovered except by animal experimentation, because without this method we should not have understood the function of the heart or the circulation, and therefore could not properly treat these conditions. The inhib-

itory action of the vagus nerve could not have been discovered, nor the action of atropin on it. The effect of atropin on the heart rate in the various species varies with the extent of vagal tone. The third and fourth uses of atropin could not have been discovered without animal experimentation. No one who is acquainted with the facts could doubt the immense value of animal experiments in the elucidation of the proper therapeutic uses of atropin and belladonna in human and veterinary medicine.

Morphin.—Let us consider another case frequently referred to in antivivisection literature—namely, that the dog can hardly be killed by morphin. This statement is partly true. The fatal dose of morphin for the dog is about thirty times larger than that for man; yet, the action of morphin on man and dog is strikingly similar on the higher centers of the central nervous system. The fatal dose of a drug does not constitute the entire knowledge of the action of a drug, nor is it the most important factor, as these writers seem to think. In physiologic laboratories, general anesthesia is usually preceded by a liberal dose of morphin to relieve the dog of the stage of anxiety and excitement when going under the anesthetic. Every laboratory man, therefore, has had ample opportunity to observe the action of morphin on the dog. The dog under a 1 grain dose passes into a condition of lazy lethargy remarkably similar to that seen in man.

A striking characteristic of morphin as a pharmacologic agent is the fact that man readily develops the morphin habit, and at the same time develops a tolerance for the drug so that a dose many times as large as the ordinary dose may be taken without producing a greater effect than the original dose. Exactly the same holds for the dog. The nature of morphin habituation and tolerance has been studied in the dog, and Faust² found that dogs

2. Faust, E. S.: Arch. f. exper. Path. u. Pharmakol.
44 :217, 1900.

behave in a manner remarkably similar to man under these conditions. Through this work on dogs, it has been found that morphin tolerance depends largely on the fact that repeated administration of the drug results in the developing by the body of increased power of destroying the drug. It is obvious, therefore, that dog and man react remarkably alike to morphin.

The Anthelmintics.—The drugs used against intestinal parasites, although the most logical for the antivivisectionist to attack, have been particularly free from their condemnation. Here we purposely select a drug for the sole purpose of killing or stunning an animal and driving him out of his natural home and habitat into outer coldness and an environment where he must necessarily die from starvation and neglect! Our conduct becomes the more reprehensible when we recall how completely these poor creatures are dependent on man and how attached they become to him, never voluntarily deserting him, no matter how dangerous or disagreeable a position he may occupy. Will the antivivisectionist here also claim that animal experimentation is of no avail? Do studies of the toxicity of anthelmintics on worms mean nothing? These are animal experiments. Owing to the lack of available material for work in this field at all times, Dr. Torald Sollmann has suggested and used earthworms as test objects.

The same anthelmintics are used in the similar infections in man and in the higher animals with equal success. For example, santonin is used in infections with *Ascaris lumbricoides* (roundworm) in both man and pig. In the field of anthelmintics, animal experimentation is essential for two reasons: to determine the toxicity of the drug (a) to the worm and (b) to the host. This yields us the "therapeutic index" of the drug.

The Digitalis Group.—In considering the debt of human medicine to animal experimentation in connection with all the drugs acting on the circulation, we must begin by stating that with-

out animal experimentation we would not know the function of the heart. We would think, as people thought before animal experimentation proved otherwise, that the arteries were filled with air and that the blood ebbed and flowed in the veins. It was through animal experimentation that we obtained correct and detailed knowledge regarding the normal circulation, and of course without such knowledge the efficient treatment of diseases of the heart and blood vessels would be out of the question.

In view of these facts, it seems hardly necessary to discuss in detail the debt of medicine to animal experimentation in connection with the important drugs acting on this system. It may be stated, however, that practically all of our knowledge of the action of all drugs affecting the circulation was obtained first through animal experimentation. It is inconceivable that we could ever have obtained a correct knowledge of the action of digitalis without resorting to this method of study. The life-saving action of digitalis in organic heart disease is one of the most striking instances of the efficacy of drugs in medicine.

The Nitrates.—The action of the nitrite series on the circulation was discovered through animal experimentation, and then applied to human medicine. The remarkable relief of an attack of angina pectoris by amyl nitrite, discovered by Sir T. Lauder Brunton,³ himself an eminent experimenter, will always remain as a brilliant therapeutic achievement. The discovery was based directly on animal experimentation. The same applies to epinephrin, the active principle of the suprarenal gland, used locally to stop hemorrhage, in certain types of shock, and to relieve attacks of asthma.

The Antiseptics.—In considering the group of antiseptic drugs, we must bear in mind that the relation of bacteria to disease would have remained unknown except for animal experimentation; and since the antiseptics are used

3. Brunton, T. L.: *Lancet*, July 27, 1867, p. 97.

to prevent the growth of bacteria or to kill them, we cannot conceive of the rational development of this type of drug without knowing anything of bacteriology.

A champion of the antivivisection cause, W. R. Hadwen, who has been addressing anti-vivisection societies in this country, has made a large number of statements regarding the use of antiseptics. There occur such statements in his addresses as the following: "I am positive that before another decade has rolled by, instead of germs being looked upon as our worst enemies, they will be looked upon as the best friends we have." In spite of his professed feelings of friendship for these germs, he objects to their being injected into man, even when their efficacy as vaccines is proved. He refers to them in other places as filth. He speaks most scornfully of the antiseptics in one place when their use was proposed by medical men through animal experimentation, but lauds their empiric use by Semmelweis because he thought that the great contribution of Semmelweis was in no wise connected with animal experimentation. As a matter of fact, Semmelweis did do animal experimentaion.

The death rate of women in the Lying-In Clinic in Vienna dropped from 11.4 per cent. in May 1847, to 1.27 per cent. the year following the practice of disinfecting the hands with chlorinated lime. A breach of technic on the part of a student, with an attendant rise of mortality to 5.25 per cent., demonstrated by human experimentation the efficacy of the antiseptic.⁴ On account of these terrible experiments on human beings, Semmelweis declined to do further animal experiments, as he regarded the result of this breach of technic as a conclusive demonstration. Certain prominent antivivisectionists writing for their cause seem to approve heartily of this terrible sacrifice of human life in the Vienna Lying-In Clinic to establish a point which could have been proved readily by a few animal experiments.

4. Sinclair, Sir Wm. J.: Semmelweis, His Life and His Doctrine; Manchester, 1909, pp. 29, 55, 63.

In other words, when antiseptics are introduced by Semmelweis through human experimentation, the antivivisectionist is in favor of them; but when they are introduced by Lister and Carrel on the basis of Pasteur's work and all those who founded the science of bacteriology through animal experimentation, he scorns their use. The same champion of anti-vivisection referred to above quotes the statement from Capt. J. Stanley Arthur, that "chlorin gas has solved the problem of a pure water supply on a large scale for the troops, and accounted for the fact that there was no epidemic of typhoid or other water-borne disease which caused such havoc in the South African campaign." He uses this in his tirade against typhoid vaccine. Apparently, the gentleman does not know that chlorin in purifying water acts as an antiseptic, killing the bacteria causing the water-borne disease, and that the amount required and the results are controlled entirely by bacteriologic methods.

IMPORTANT APPLICATIONS OF THE SIMILARITY OF REACTION OF ANIMALS AND MAN TO DRUGS

The statements made in antivivisection literature that the animals react entirely differently from the human being to drugs is further refuted by three outstanding facts:

1. Canary birds are used by miners the world over for the detection of the gas known as carbon monoxid. This substance is a very poisonous gas which combines with the red coloring matter of the blood—hemoglobin—and replaces the oxygen carried by this pigment, forming carbon monoxid hemoglobin. This robs the blood of its most urgent function—the carrying of oxygen from the lungs to the tissues—and results in death when the blood is about 80 per cent. saturated with the gas. This gas is present in many mines, and active ventilation of the mines is required to keep the concentration down below the danger point. All the higher animals have hemoglobin in their blood and react to carbon monoxid in precisely the same way that man does. All

animals below the vertebrates, which do not depend on hemoglobin for the transport of oxygen, are totally unaffected by the gas. Birds, because of the large volume of air breathed per unit of body weight, and because of their small size and small blood volume, become affected by carbon monoxid before man, and when the miner observes that his canary bird is lying down instead of perched up as normally, he realizes that the air is not suitable for the support of life and he makes a hasty exit for clear air. If he reaches wholesome air in time, the bird revives—if not, the bird dies. Would the antivivisectionist deny the miner this security which animal experimentation has given him in order to protect the bird against the possibility of death by asphyxiation?

The mouse was formerly used as an indicator for carbon monoxid, but the difference in the attitude of a normal mouse and one suffering distress is not so readily observable as in the case of the bird. This use of animals would be obviously impossible if animals and man responded utterly differently to chemicals, whether drugs, which in proper dosage are useful in the restoration of health, or poisons.

2. Before the rise of toxicology, which made the detection of poisoning almost certain, people lived in dread of being poisoned by their enemies. This dread was particularly pronounced among important personages, the royal families, and persons prominent in the affairs of church and state. It was then a common practice to have the cooks or servants first partake of the food, and frequently the food was fed to animals when there was reason for believing that it might contain poison. Instances of the recognition of the similarity in the action of food and poisons on man and on animals are found in ordinary literature.

In "The Swiss Family Robinson" we find the statement, "As a rule we may consider any kind of vegetable or fruit eaten by birds or monkeys as wholesome"; and, again, the father of the family suggests that the edibility of the figs be tested on the pet monkey before eating

them. This book, by a medical layman, which breathes a spirit of kindness to animals, therefore suggests the use of animal tests in determining the action of unknown materials on man, and represents the opinion which would be given by any layman with common sense.

Similarly, the toxicologist of today, when searching for an unknown poison in a dead body, administers a small amount of the supposedly toxic material to a small frog in order to determine the presence or absence of any poison in it.

3. If any final proof were needed that drugs act very similarly on man and the higher animals, it is furnished by the fact that many drugs are standardized by biologic methods—i. e., testing on animals. The active principles of certain important drugs cannot be quantitatively determined by chemical means with the desired accuracy. The most important instances are the drugs of the digitalis series, the drugs acting on the uterus, and antitoxins, vaccines and serums.

The digitalis drugs are used in the later stages of organic heart disease, often prolonging the patient's life and enabling him to return to the ordinary duties and pleasures of life. When this drug is administered, the physician must know that the particular specimen is not inert, that it has the power to do that which is expected of it, and finally what dose of the particular preparation is required. This can be ascertained only by experiments on animals or by its use at the bedside when human life lies in the balance, with the family watching the experiment and the fate of the family at stake.

The action of digitalis on the frog and on the cat is sufficiently like its action on man to enable us to determine its potency as a cardiac drug and to determine its dosage. In the frog, the digitalis bodies act also on the muscle of the heart, increasing the contractions, and by determining the amount required to bring the heart of a 20 gm. frog to systolic standstill in

exactly one hour, we learn the potency of the drug for man also.

Ergot and pituitary extract are used to prevent hemorrhage following childbirth. Not infrequently following delivery, the uterus fails to contract and remains flabby and dilated, and severe bleeding results. The two drugs that are most used to bring about contraction of the uterine muscle, thereby constricting the blood vessels and stopping hemorrhage, are ergot and extract of the posterior lobe of the pituitary gland. Here also the active principles cannot be quantitatively determined chemically, and again we are forced to resort to biologic testing. In this case, the best test object is the uterus of the virginal guinea-pig. The action on the uterus of the guinea-pig is the same as on the human uterus—the drug causes contractions of the uterine wall. Surely, the antivivisectionists would not have us determine the potency of the drug on the young mother, nor would they take the responsibility for the loss to the husband and new-born for the ebbing away of the mother's life because the preparation of the drug was inert. The same conditions obtain in determining the potency of diphtheria antitoxin and other antitoxins. Here, again, in the absence of animal experimentation we should have to determine whether or not the antitoxin was active on the child sick with diphtheria. How many persons would consider such a procedure in the case of their own child?

With this evidence, the reader may decide whether the effects of drugs on animals and man are so utterly dissimilar as to render such studies useless. In the light of these facts, consider for a moment the responsibility which the antivivisectionist assumes toward you and me and all mankind in urging the abolition of animal experimentation.

THE DEPENDENCE OF PHARMACOLOGY ON ANIMAL EXPERIMENTATION

In order to give a more general picture of the importance of animal experimentation to the science of pharmacology, a few of the

fundamentals of the subject which have been established may be briefly referred to.

Pharmacology is that phase of biologic science which deals with the action of chemicals or mixtures of chemicals on living things. It is therefore a fundamental branch of medical science, and is an important study in every medical curriculum. In its relation to medicine it deals largely with substances that are useful in human therapy. In its relation to veterinary medicine, emphasis is laid on drugs and poisons important from the point of view of that subject.

Pharmacology has largely furnished the basis for the scientific use of drugs in the curing of diseased conditions, the alleviation and prevention of pain, and the prolongation of life. These are the basic problems with which it deals. As a by-product, pharmacologic work often leads to important contributions in the field of normal function; i. e., physiology. Again, pharmacologic work often leads to important advances in pathologic physiology, and thereby elucidates the subject of functional derangements in disease. The subject includes structural changes in the body as a result of chemical agencies, chemical changes in the drug as a result of its passage through the body, and the relation of chemical constitution of drugs to pharmacologic action. The term "pharmacology" is sometimes used in a somewhat narrower sense by restricting it to the alteration of function by chemical means. In the treatment of disease by drugs, we are concerned with the alteration of abnormal function by chemical means.

The cells of our bodies are bathed in a fluid—lymph—derived from the blood and tissues, which insures a free interchange of material between blood and tissues. The body cells of the higher animals live in a fluid medium as truly as do single-celled forms which live in the ocean. All animal experimentation shows that life depends on the maintenance of a certain physical and chemical environment. The administration of any drug that brings about a

change in the functional activity of the cell must do so in consequence of a change in the chemical environment of the cell. In order to understand this change it is necessary to understand the normal chemical environment of the cells of our body. The body of facts concerning the normal chemical environment constitutes the subject of physiologic chemistry.

Changes in the chemical environment of the cells of the body are of two types: (1) negative and (2) positive, the two being equally definite. A negative change in the chemical environment is brought about by a reduction of dosage or entire withdrawal of something that has become a factor in the chemical environment and therefore a substance to which the cell has become accustomed. Thus, a decrease in the supply of oxygen causes striking symptoms or even death. The withholding of food from the animal, the withholding of cocaine, morphin, alcohol, coffee and tobacco from the body habituated to these drugs, or the withholding of the vitamins from the diet are all instances of a negative change in the chemical environment which brings about more or less striking changes in the functional activity of the cells.

A positive change in the chemical environment results every time an active drug is administered. The administration of a definite dose of a drug may produce changes in the functional activity of different intensity according to the mode of administration. The intensity of action of a drug depends on the concentration in which it reaches the particular cells on which it acts, and the duration of time that this concentration is maintained. The concentration which a drug reaches in the body is a function of two factors: (1) the rate of absorption, and (2) the rate of its removal from the body. Drugs are removed from the body by two general methods: (a) excretion, and (b) chemical destruction in the body.

Thus, a drug administered by mouth is usually absorbed more slowly than if administered subcutaneously or intravenously, and in this case the intensity of action is determined

by the rate of absorption. If the rate of absorption drops below the rate of removal, the drug has no effect in the body because a sufficient concentration is not obtained. Therefore, it is very important for us to know the rate of absorption of drugs when administered by any of these routes. None of this information applicable to all cases of drug action could have been obtained without animal experimentation. The very rudiments of the subject could not have been elucidated.

Starting about thirty years ago and lasting for a period of ten or fifteen years, there was a general state of mind among physicians that there were few drugs valuable in the treatment of disease. This period of drug nihilism served a most useful purpose because the existing knowledge of the use of drugs, many of which had been handed down through the ages, was unreliable and there was a sort of blind confidence in the efficacy of drugs which resulted of necessity in disappointment when they were critically used. Within the last fifteen or twenty years, there has been great progress made in the treatment of disease. The increase in the amount of animal experimentation has placed the use of drugs on a much firmer basis. Nearly all valuable new drugs have been introduced by the route of animal experimentation, the only noteworthy exception being chaulmoogra oil, the use of which in leprosy was determined in human beings without preliminary animal experimentation because leprosy is a disease which cannot be given to animals. The latter fact is probably responsible for the great delay in finding adequate treatment for the disease.

Animal experimentation has resulted in increasing the usefulness of old drugs. It has also been extremely useful in discarding drugs that are useless and in clearly defining types of cases in which a given drug is indicated and may be of service. The result of all the work that has been done is that drugs are used today in a much more scientific way than formerly, and drugs are not expected to accomplish what

is impossible. Thus, in degenerative diseases in the course of which specialized tissue has actually disappeared as a result of disease processes and has been replaced with inactive scar tissue, and when such loss of tissue produces symptoms, it is vain to hope to restore the lost tissues by drugs. The use of drugs in such conditions is as futile as would be an attempt to cure a wooden leg or a glass eye, by drugs. The proper use of medicines, therefore, presupposes an accurate knowledge of the pathology of the disease, in regard to structural changes both in the tissues and in their function.

Let us take up a single instance of how animal experimentation has greatly improved the therapeutic use of old drugs. Digitalis was introduced into medicine by Dr. William Withering in 1785 for the treatment of dropsy. Clinicians at various times urged its use in various conditions, a partial list of which would include apoplexy, rapid pulse, inaccessible hemorrhage, tuberculosis, tuberculous hemorrhage, inflammatory fever, malaria, neuralgia, epilepsy, hemicrania, general paresis, delirium tremens, menorrhagia, uterine atony and typhoid fever.⁵

Digitalis was in general use for seventy-five years before its action was studied by the method of animal experimentation. In spite of all these years of clinical use, the views held by medical men regarding its action were in many important respects entirely erroneous, and its field of therapeutic usefulness was not clearly defined, as the list of conditions in which it was recommended clearly indicates. Thus, in 1860, Clarus⁶ stated that digitalis slows and weakens the heart. Animal experimentation with this drug started about this time, and as a result the therapeutic use of digitalis now is strictly limited to the condition

5. Brunton, Sir T. Lauder: Collected Papers on Circulation and Respiration; London, 1907. First series p.32.

6. Clarus: Handbuch der speciellen Arzneimittellehre, 1860.

in which it can definitely be proved that it is of service—namely, to relieve or prevent decompen-sation in heart disease and to relieve acute cardiac breakdown. The drug greatly strengthens contractions of the heart muscle. This we know by direct observation, and this knowledge could not have been reached without animal experimentation. In the other conditions its use has been virtually abandoned. In the same manner, many useless drugs have been eliminated, and the sphere of usefulness of many worth-while drugs has been accurately defined so that positive proof exists of their usefulness, each in its own field.

THE PURPOSES FOR WHICH DRUGS ARE USED

Drugs are used in medicine for four main purposes: (1) to cure; (2) to relieve; (3) to diagnose, and (4) to prevent disease.

The curative drugs actually remove the cause of the disease. They are sometimes referred to as specific drugs. A list of the best recognized curative drugs is given in Table 2.

TABLE 2.—CURATIVE DRUGS

Drug	Disease
Quinin.....	Malaria
Mercury.....	Syphilis
Arsphenamin.....	Syphilis
Neo-arsphenamin.....	Syphilis
Arsanilic acid.....	Trypanosomiasis
Chaulmoogra oil.....	Leprosy
Emetin.....	Amebic infestation
Oil of chenopodium.....	Hookworm infestation
Thymol.....	Hookworm infestation
Santonin.....	Roundworm (<i>Ascaris lumbricoides</i>) infestation
Pelletierin.....	Tapeworm infestation
Thyroid gland (thyroxin).....	Cretinism, myxedema and milder forms of hypothyroidism
Diphtheria antitoxin.....	Diphtheria

The palliative drugs are used to relieve symptoms of disease and often thereby prolong life. The most important of this group of drugs are given in Table 3.

The drugs used to relieve or to prevent pain include the general and local anesthetics, opium, morphin, codein, scopolamin and analgesics of the acetanilidacetysalicylic acid groups.

Drugs used to meet special emergencies include ergot and preparations of the pituitary gland, to prevent hemorrhage following childbirth, and iron salts, to cause a rapid regeneration of blood in chlorosis and secondary anemia.

Drugs used for diagnostic purposes include tuberculin, principally in veterinary medicine; phenolsulphonephthalein, in tests for kidney efficiency; atropin sulphate, in cardiac arrhythmias and functional spasm of the pylorus, and several others used less frequently.

TABLE 3.—PALLIATIVE DRUGS

Drug	Most Important Uses
Digitalis group....	Decompensated heart disease
Purgatives.....	Constipation, to rid body of excess of fluid
Camphor.....	Cardiac embarrassment
Epinephrin.....	Shock, hemorrhage, asthma
Nitrites.....	Especially amyl nitrite in angina pectoris
Diuretics.....	To increase secretion of urine
Arsenous oxid.....	Pernicious anemia
Glucose.....	To prevent acidosis
Soporifics.....	To promote sleep; in certain types of convulsions
Atropin.....	To prevent vagal stoppage of heart; decrease secretions; relax bronchioles; mydriatic
Strychnin.....	To stimulate respiratory center
Bromids.....	Epilepsy
Phenobarbital.....	Epilepsy

Drugs used to prevent disease include the iodids, to prevent the development of goiter; tetanus antitoxin, to prevent lock-jaw; diphtheria antitoxin, to prevent diphtheria, and vaccinations, to prevent smallpox, typhoid fever, etc.

In many instances the use of the palliative drugs saves life by tiding over a crisis and enabling the natural forces tending to restore the normal to become operative.

The great clinician Sydenham said, "Without opium few would be callous enough to practice therapeutics." It is essential that the physician be able to control pain, since pain is most exhausting. The recent work on shock has emphasized that severe pain itself is inimical to the return of the normal state.

ROLE OF ANIMAL EXPERIMENTATION IN THE INTRODUCTION OF A NEW DRUG

The rôle of animal experimentation in the introduction of a new drug into human or veterinary medicine should be presented: In order to have a concrete example before us we shall take a new arsenical drug which some investigator conceives will be a better drug than any known in the treatment of syphilis. Let us begin with Ehrlich's drug arsphenamin, which was introduced about 1910, in the treatment of syphilis.

Ehrlich started out with the information that an organic arsenical compound known as atoxyl is useful in the treatment of diseases caused by trypanosomes, such as trypanosomiasis (South African sleeping sickness). The trypanosomes are biologically closely related to *Spirochaeta pallida*, which is the infectious organism in syphilis. Trypanosomiasis is virtually always fatal if untreated. Atoxyl possesses certain disadvantages, however, in that in certain cases it causes impairment of vision or even blindness. Ehrlich found that atoxyl has no action on the organisms in question when they are exposed to the drug in the test tube. In the infected animals (rats, mice and fowl), the drug has a definite destructive action on the parasites.

Ehrlich and his colleagues then began to make a series of chemical derivatives of atoxyl, producing in all nearly a thousand substances. The six hundred and sixth substance, known as arsphenamin, had outstanding value in the treatment of animals experimentally infected with syphilis (rabbit), trypanosomiasis (rat and mouse) and spirillosis (fowl). The next point which had to be elucidated by Ehrlich and his coworkers was the so-called therapeutic index; namely, the ratio of the curative dose to the maximal tolerated dose. For a drug to be useful in medicine there must be a sufficient margin of safety between the dosage which will be beneficial and that which will do harm. This ratio again must be worked out

on animals. Following this part of the study, the toxic dose of the drug is determined in a series of animals—rabbit, guinea-pig, white rat and white mouse. The data thus obtained enable one to arrive at the surely safe dose which may be used in the first studies in human therapy. The pathologic changes in the tissues produced by toxic but nonfatal doses of the drug in animals must next be studied in order to determine the point of attack of the drug in the body so that in the first cases of therapeutic use in which it is studied we shall know exactly what type of symptoms to look for if the drug exercises any toxic effects. Some drugs in toxic doses manifest their first effects on the circulation, others on the nervous system, the skin, digestive organs, or the kidneys, etc.

In this manner we may focus our attention in the early therapeutic study in man on the organs likely to be attacked, and by appropriate tests detect the very earliest sign of any deleterious effect. In this way a drug may be excluded in human medicine if it is too dangerous—that is, if there is not a sufficient margin of safety between the therapeutic and toxic dosages without injuring a single individual. Without the preliminary animal experimentation it would be impossible to know where a drug would act or what drugs were worthy of study in human or veterinary medicine. No man who had the proper feeling toward his fellows could be induced to make such a study at the present time without the information to be obtained by animal experimentation.

The statement is frequently made in anti-vivisection literature that "the last experiment must always be on man." The foreknowledge gained from animal experimentation is of as much value as are the laboratory tests made to determine the strength of new materials used in the construction of a bridge. The final experiment is made when the bridge is built and in use; the preliminary tests must be made in the laboratory to learn the strength of the

materials and whether there is any probability of success. No engineer would think of using untested new materials. Surely those opposed to animal experimentation would hesitate to recommend that tests of new drugs be made on the human being without previous trials on the lower animals.

With all this preliminary information, animal experiments would still have to be done to determine the chronicity of the lesions produced by a toxic dose of the new arsenical drug in order to know what period of time should elapse before repeating a dose for therapeutic effects. It is essential that the repetition of doses be spaced so that there will be no accumulation of toxic effects. Finally, after a drug has been successfully introduced, it is necessary in the case of arsenicals to control each batch of the manufactured product to make sure that every step in the process is properly controlled. Therefore, the toxicity must be tested on animals, or human life would occasionally be sacrificed.

It is variously estimated that from 5 to 10 per cent. of the population have syphilis. This disease menaces the next generation, and it is of inestimable importance to control its ravages. There is no field of medicine in which animal experimentation is more important for progress or in which the results have conferred greater benefits on man. The future in this line of endeavor holds even greater promise that this scourge will be conquered.

It should always be borne in mind that some of the greatest discoveries in therapeutics are the outcome of pure research undertaken with the thought of increasing the bounds of biological knowledge but without the thought of immediate application; but this is not always the case.

Sir T. Lauder Brunton,⁷ an eminent physician and an ardent animal experimenter, wrote, in 1867: "Few things are more distressing to a physician than to stand beside a suffering

7. Brunton, T. L.: *Lancet*, July 27, 1867.

patient who is anxiously looking to him for that relief from pain which he feels himself utterly unable to afford. His sympathy for the sufferer, and the regret he feels for the impotence of his art, engrave the picture indelibly on his mind, and serve as a constant and urgent stimulus in his search after the causes of the pain, and the means by which it may be alleviated." Brunton had in mind the patient suffering from angina pectoris, an agonizingly painful disease of the heart, and he introduced the use of amyl nitrite, which often affords magical relief. The introduction of this drug by Brunton was the direct result of animal experimentation. Similarly, the observation of human suffering at the bedside and the depth of sympathy felt by the physician is often the direct stimulus for investigation involving animals. The physician's sympathy in these cases does not take the idle form of such phrases as, "Too bad; I am sorry, but we must save the guinea-pigs." He leaves the bedside with the determination to be able to control the next such situation which arises, and to bestow the blessings of relief for which his profession stands. He knows full well that to accomplish his purpose means energy, hard work, ingenuity, ability to stand up under disappointments, financial loss and self sacrifice. All these obstacles he is ready to face; they are inevitable, and he knows it. But there is a form of obstruction which he ought not to have to encounter. It is the opposition of persons who are either fanatical or misinformed on the subject of animal experimentation. Among the former one often sees individuals with an excess of money and leisure and no legitimate outlet for their energies, who either have no conception of the mass suffering of the race, or are totally callous to it, who seek to interfere with his noble purpose and to revile him, his methods, and his purposes, to the uninformed public through falsehood and calumny. Attempts to convince such persons of the legitimacy and propriety of animal experimentation have been and probably always will be

fruitless; but, as already intimated, there are other individuals who have taken this matter up largely because of the misrepresentations perpetrated by their fanatical colleagues. It is to this misinformed class and to the uninformed public that the experimenter must appeal, and in so doing he feels that their intelligence and rational philanthropy will be ready to meet him half way and result in a complete understanding.

Forget for a moment that the methods of animal experimentation have given us practically all of our knowledge of physiology and hygiene, the science of bacteriology, aseptic surgery and local anesthesia; and have greatly contributed to the knowledge and safety of general anesthesia, and the proper use of most of our drugs. In brief, let us suppose that the methods of animal experimentation had not added immensely to our knowledge of human and veterinary medicine and practically rid the world of Asiatic cholera, yellow fever, bubonic plague and many terrible epidemic diseases affecting animals. On this supposition, let us imagine that a physician sees a patient suffering with general paresis resulting from an accidental and innocent infection with syphilis years previously. He knows that the mental impairment if untreated will be permanent, that the family will lose a valuable member and will be stigmatized by having a member die in a hospital for the insane, and that the marriageability of sons and daughters will be interfered with. Suppose this physician begins an investigation involving animals in the determination to find a way of treating or preventing the development of this disease, believing that animal experimentation had never up to that time accomplished anything. Should he be helped or hindered in his work? Let those who suffer answer; or, if they cannot, let those who see them and render all aid within their knowledge answer for them. But do not allow the answer to be given by those who are ignorant and refuse to be informed, and who lead such happy lives that they never come in

contact with anything more pitiable than a dumb animal. Their opponents see poignant human suffering all the day and every day. The ideal and logical solution would be to let each group turn its attention to the relief of the type of suffering that it sees. The medical experimenter is unalterably opposed to wanton cruelty wherever found, and will lend moral and financial support to any movement directed against it. The only conflict that exists is that those in favor of animal experimentation demand that the lives of a few animals may be sacrificed in the most humane manner possible for the benefit of the human race and the remainder of the animal world. The proposition may be briefly stated in this way: Every new drug must have its first trial. Shall this first trial be on man or on animals? Each must answer this question for himself; but the answer must be made with the full knowledge that drugs act very similarly on man and on animals.



